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COMPLICATIONS ARISING IN DONORS IN A MASS BLOOD PROCUREMENT PROJECT

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The Blood Donor Service of the American Red Cross has been in operation since February, 1941. As of April 1, 1944, over 7,000,000 pints of blood have been collected from volunteer donors throughout the United States to be processed into dried plasma and serum albumin for the Armed Forces. This amount of blood represents donations from approximately 3,500,000 individuals, since the re-donor rate is now about 50%. The average weekly bleedings obtained approximate 103,000; the various Centers, depending on their respective capacities, handle from 1500 to 9000 donors weekly.

It is immediately obvious that an unprecedented opportunity is presented to compile and analyze the effects of this mass blood procurement project on the donors and to note especially the complications and problems attendant upon such a program. It has been the customary procedure, since March, 1942, to require that each Donor Center file with the National Office a monthly report which includes, along with the general statistics, a report of the reactions, complications, and accidents that have occurred during the previous month. Previous to that time, when only a very few Centers were in operation, detailed reports of all complications and accidents were filed by letter in the National Office as they occurred. From these reports, as well as from several special studies noted below, this survey has been made. In view of the increasing general interest in blood banks, especially for smaller hospitals and institutions, it is hoped that this report may be of some value to those concerned with the organization of such blood banks and may aid in anticipating some of the problems which arise from time to time in the maintenance of such projects.

The first consideration of the Blood Donor Service has been the care

and protection of the donor; the second has been the care and prevention of spoilage in the blood obtained. The achievement of the first objective must be based on 2 factors: (1) a controlled basis of operations throughout; (2) a rigid eligibility standard for all donors.

The methods of operation and the donor requirements have been discussed in previous papers.[8]

It has been the experience of the Blood Donor Service that the accidents and complications which may occur can be classified roughly into 4 groups: (1) those related to the mechanics of the venepuncture, and including those occurring during the examination and preparation of the donor; (2) those occurring as a general systemic reaction and including all consequences thereof; (3) those occurring as late, delayed, or prolonged reactions; (4) those occurring as coincidental or unrelated accidents, but approximating the time of the donation.

Group 1. The complications and accidents under this heading, with the exception of hematomata, constitute the smallest group. The number of reactions at this point in the procedure has considerable bearing on the personalities and techniques of the personnel handling the donors. As would be expected, there have been a few individuals who, through fright or nervousness, have fainted when the finger was pricked for a hemoglobin test, or who have bitten the thermometer when the temperature was taken. Reactions at this point of the procedure apparently have little or no adverse psychologic effect on other donors awaiting their turn.

Of the more serious incidents, there were 2 reported instances of infected fingers following punctures for hemoglobin determinations and 1 reported case of a felon followed by an osteomyelitis of the terminal phalanx of the finger.

In the preparation of the arm, soap, water, aqueous iodine (2%), and alcohol are used. The possibility of iodine burns is therefore slight. A 1% solution of novocaine or procaine-HCl has been used routinely as a local anesthetic prior to the insertion of the 15 gauge needle into the vein. In this connection 3 unfortunate, though not serious, incidents have occurred. In one Center, the use of a commercially-prepared solution of a local anesthetic, other than those referred to above, resulted in the formation of a small (1 cm.) area of local ulceration and subsequent slough. Use of the solution was promptly discontinued. In another Center, 1% sodium hydroxide was inadvertently substituted for novocaine in filling containers for sterilization. A similar error was made in the third case when 1% merthiolate was prepared in place of novocaine. Local reactions, similar to those noted in the first instance, resulted, all of which healed promptly with appropriate therapy. A few cases of a local reaction to novocaine have been reported.

A small number of individuals have exhibited a local sensitivity to the resin in the adhesive dressing which is used in most of the Centers to cover the site of the venepuncture. This has been especially noticeable among individuals who have neglected to remove the dressing at the end of the specified 24 hours.

Complications attendant upon the actual venepuncture comprise the majority of difficulties in the first group. No matter how skilled the operator, there will be technical difficulties which will result in a certain minimum number of complications directly related to the mechanical procedure of the venepuncture. It has been the policy of the Blood Donor Service to accept all donors, regardless of whether or not suitable veins were apparent. In approximately 1% of the donors the venepuncture has been classed as "unsuccessful" (*i. e.*, less than 350 cc. of blood has been obtained). Venepunctures are done by physicians or by nurses trained and qualified in this technique. It is a rule that no donor is "stuck" more than twice, regardless of whether one or both arms are used, and the venesection is discontinued whenever it is apparent that a large hematoma may develop. In this latter case the donor is informed that the arm may be discolored and painful, and is advised as to the symptomatic treatment required.

In a study of 40,000 donors, which is summarized in Table 3 and which will be reported in detail below, 10% of the donors indicated some pain, soreness, and/or discoloration in the arm from which the blood was withdrawn. These complaints ranged from slight discoloration or discomfort to an inability to use the arm for several days or more. This complication is unfortunate and often disturbing from the donor's point of view, but aside from a few instances, the discomfort has been minor and temporary. A number of cases have been reported in which the donors have complained of severe, persistent pain on motion of the elbow or shoulder at intervals varying from a few days to several weeks after the blood was withdrawn. In 8 of these cases, a definite diagnosis of bursitis was made, either radio-humeral, olecranon, or subdeltoid, depending on the location. In all of these cases a hematoma had existed prior to the development of the symptoms, and in 3 of the cases in which an actual bursitis developed, and in which calcium deposits were noted on Roentgen ray, a previous history of the same condition in the same joint was obtained. It is probable that the donor's natural reluctance to use the arm, following the development of the hematoma, aggravated a previously existing condition. In other cases the actual deposit of blood around the joint resulted in symptoms closely simulating a true bursitis. A few cases have been noted in which a complaint of severe pain in the arm or shoulder developed subsequent to a hematoma and in which Roentgen ray of the joint involved indicated a preëxisting hypertrophic arthritis with similar radiographic changes in the corresponding joint of the other arm. Here again the natural limitation of motion coincident with the existing hematoma undoubtedly aggravated an underlying subclinical condition. In 1 or 2 of the cases exhibiting these symptoms, the diagnosis of hysteria must be considered, in that no explanation for the prolonged discomfort could be found on repeated examination and Roentgen ray.

In the experience of the Service to date, there have been approximately 15 reported instances of a local abscess formation at the site of the venepuncture, in addition to those noted above as a result of

a faulty local anesthetic, and 3 reported cases of acute cellulitis of the inner aspect of the arm above the fossa. There have been 13 reported cases of a thrombophlebitis of one of the veins of the antecubital fossa, 1 of which was migratory through several branches of the median basilic vein over a period of several months. In addition there have been 2 cases of migratory phlebitis originating in the vein from which the blood was withdrawn and later involving the leg veins. In 1 of the latter cases the donor had had a previous history of thrombophlebitis. One donor developed a transient staphylococcus septicemia 48 hours after donation. He recovered after being hospitalized for 5 days.

Group 2. In this group the majority of reactions that occur can be classed as "faints" with a subheading of "the consequences thereof." Syncope in blood donors has been and probably always will be a major problem in any donor organization. Careful selection and examination of each individual donor as well as a reassuring attitude on the part of all personnel in direct contact with the donor will do much to lessen the apprehension with which many individuals approach a blood donation for the first and even successive times. In spite of these precautions a certain percentage of donors will have some form of reaction ranging from a mild presyncope to a true shock. Various estimates have been made of this percentage. Poles and Boycott[6] state that 2.8% of 10,000 donors showed "true" syncope. A Report to the British Medical Research Council[7] gives a figure of 5.5%, using the term "faints" to include all donors in whom "the symptoms and signs associated with fainting were sufficient to delay or alter the normal procedure." A study of 16,000 volunteer Red Cross donors in Atlanta, Ga.,[4] gave a total syncope rate of 4.2%, whereas in a survey of 40,000 consecutive donors in 4 other large Red Cross Centers, a figure of 8.9% was obtained as indicating the number of donors who had *any* immediate reaction following the donation. This is a figure based on a subjective estimate by the donor and represents positive answers to the question, "Did you have any ill-effects immediately following the donation?"

A number of surveys have been made from time to time on Red Cross volunteer donors in an effort to obtain information on a number of factors which might have bearing on reactions of this type, and to determine what group of individuals will experience syncope under what conditions. The majority of the figures referred to below were collected in a punch-card survey made in 6 different Centers throughout the country. Identical forms, a sample of which is printed below (Fig. 1), were sent to these Centers and a total of 5032 cards were returned, in which there were 2294 reactors, and 2738 nonreactors used as controls. These cards were filled out by the regular nurses attending the donors during the venesections. A smaller survey on a somewhat different basis was made in a single center on 2521 donors, 570 reactors and 1951 controls.[1] The results on these 2 surveys have been combined as far as possible, and the conclusions listed in Paragraphs 1 to 13 below. There would appear to be so many factors involved and so many possibilities to be considered that

statistical results can hardly be considered accurate. However, certain impressions have been gained and certain generalities may be stated.

FIG. 1.—CARD REQUESTING INFORMATION

AMERICAN RED CROSS BLOOD DONOR SERVICE

1-4 NAME _____ DATE _____ SERIAL NO. _____

5 SEX _____
AGE _____
WEIGHT _____
7 Light
8 Medium
9 Heavy

6 *Donation—No.*
y Previous fainting—yes
x no

7 *Occupation*
y Clerical, executive, professional
x Manual
0 Housewife
1 Other, specify _____

History
3 Recent illness, specify _____
4 Menstruation—absent
5 present
6 week before or after
7 other part of cycle
8 History of fainting
9 of convulsions

8 *Psychologic Factors*
1 Friend or relative in Armed Service
2 Reaction of friend to donation
3 Other faints in room
4 Prolonged wait before donations
5 General apprehension
6 Ease of venesection
7 Other pertinent history

9 Last food—hrs. since _____
y heavy meal
x prescribed food
10 Work—hrs. since _____

11 Work
1 light
2 hard
3 indoor
4 outdoor
12 Last sleep—hrs. since _____
13 duration in hrs. _____

14 *Type of Reaction*
1 None
2 Mild or transient
3 Prolonged with minor symptoms
4 Severe collapse

15 *Point of Reaction*
0 Before donation
1 In bleeding room—before
2 during bleedings
3 after bleeding
4 In canteen—before eating
5 after eating
6 hot nourishment
7 cold nourishment
8 smoking
9 Delayed—specify place

16 Amount bled _____ cc.

17 *Symptoms*
y Pallor
x Perspiration
0 Loss of consciousness
1 Nausea
2 Vomiting
3 Cramps
4 Twitching
5 Tetany
6 Incontinence
7 Hysteria
8 General convulsions
9 Other, specify _____

The reverse side of the card provided space for entries on the donor's temperature, pulse, and blood pressure, and for outside temperature, barometric pressure, and humidity.

1. *Classification.* All reactions were classified as (1) mild or transient, (2) prolonged or severe. Loss of consciousness was not felt to be an adequate basis for distinguishing a mild from a severe reaction. A donor may lose consciousness momentarily, yet recover so rapidly that the reaction may be considered transient, whereas another donor may appear initially to have only a mild presyncope, but ultimately develops a reaction that is unduly prolonged and alarming. The group classed as "severe" includes all donors who have exhibited generalized convulsions with or without tetany. In general, mild or transient reactions comprise 88% of the total, and the severe reactions, 12%. The same grades of reactions are apparent in both new and redonors.

2. *Sex.* The ratio of males to females in those who react is about 1:1.5; the ratio of males to females in the entire donor group is 4:5.

3. *Age.* The proportion of reactions is highest in females under 21 years. Under 40 years of age in both males and females reactions

were higher in proportion to the total number of donors than in the group over 40 years of age (*i. e.*, 71% of the reactions occurred in 61.2% of the donors under 40 years of age). The more severe grades of reactions, however, occur more frequently in the older age groups.

4. *Number of Donations.* The incidence of reactions is from 3 to 4 times greater in first donors than in redonors. This is to be expected, both because of self-selection and because donors who have had a marked reaction are requested not to return.

5. *Weight and Body Build.* In both male and female donors weighing under 120 pounds the incidence of reactions is about twice the usual expectancy; this ratio diminishes gradually until, over 150 pounds the actual ratio is less than the expected. About half of the "severe" reactions occur in so-called "light females." In the entire donor group, 56% of all first donors were classified as "light," whereas in the redonor group only 15% were in this category, which would indicate a certain degree of self-selection, considering the fact that approximately 80% of all reactions occur in the first-time donors.

6. *Occupation.* Among males in the so-called "white collar class," the proportion of reactors is slightly higher than among the other groups; the same is true for women. There is slight evidence to indicate that those who are normally engaged in strenuous physical labor are less likely to develop reactions.

7. *Temperature, Humidity, Time-of-day.* The impression is widespread that more reactions occur on warm, humid days; this cannot be confirmed statistically. However, on any day in which there has been a sudden change in the temperature, the number of reactions is noticeably increased. There is slight evidence to indicate that there are fewer reactions during the morning hours; this, of course, is linked closely with the increasing fatigue of the later hours of the day.

8. *Food, Rest, and Sleep.* There is no statistical correlation as to these factors among those who react. Only in the extreme cases does lack of food or sleep appear to have any bearing on the development of a reaction.

9. *Blood Pressure and Pulse Rate.* There appears to be little correlation between the pulse rate and those who react, as opposed to those who do not. There is definite evidence to indicate that hypotension predisposes to reactions. With systolic values less than 110 mm./Hg before donations, the incidence of reactions is $2\frac{1}{2}$ times greater than was to be expected.

10. *History of Fainting.* This is an important predisposing factor among those who react. In a group of 5000 donors, 18% of the reactors and only 3% of the non-reactors had a history of fainting under other circumstances.

11. *Psychologic Factors.* One of the outstanding factors predisposing to syncope is apprehension. In the group noted in Paragraph 10 above, 7% of the controls admitted to or showed apprehension prior to the donation, whereas this was noted in 30% of those who reacted. This finding is equally true for men and women, and, as would be expected, is overwhelmingly characteristic of first donors. The pres-

ence of other reactions in the room is a disturbing factor twice as often in the reactors as in the non-reactors.

12. *Point of Reaction.* About 1% of all reactions occur before the donor enters the bleeding room; 50% occur in the bleeding room during the donation; 20% in the bleeding room after the donation; the remaining 29% occur while the donor is in the canteen or preparing to leave the Center. It is of interest to note that in this latter group, reactions are 10 times as frequent following hot nourishment, such as coffee as after other liquids. This, however, is undoubtedly explained by the fact that the majority of donors will take coffee following the donation in preference to other liquids offered. The incidence of delayed reaction, *i.e.*, outside the Center, is about 0.1%.

13. *Symptoms.* The symptoms encountered are listed below in order of frequency as determined in one series of 2294 "reactors." A combination of symptoms occurred, of course, in many of the donors. It is of interest to note that the more severe symptoms encountered, such as loss of consciousness, nausea, vomiting, convulsions, and tetany, occur more frequently in women.

TABLE 1.—SYMPTOMS ENCOUNTERED IN SYNCOPE IN ORDER OF FREQUENCY

	Total, 2294		Males, 927		Females, 1367	
	No.	%	No.	%	No.	%
Pallor	2139	93.24	887	95.69	1252	91.59
Perspiration	1588	69.22	722	77.89	866	63.35
Nausea	638	27.81	210	22.65	428	21.31
Loss of consciousness	253	11.03	92	9.92	161	11.78
Vomiting	105	4.57	20	2.16	85	6.22
Convulsions	78	3.40	25	2.70	53	3.88
Twitching	48	2.09	16	1.73	32	2.34
Cramps	43	1.88	11	1.19	32	2.34
Tetany	22	0.95	6	0.65	16	1.17
Incontinence	11	0.47	4	0.43	7	0.51

All of the above generalizations agree with the findings in the British Report to the Medical Research Council referred to above. An attempt to draw any statistical conclusions on either the constitutional or physical factors which predispose to fainting is difficult. Aside from the obvious fact that a history of previous fainting and an admission of apprehension on the part of the donor predisposes to a reaction, definite conclusions may not be drawn. The impression is obtained that fainting in donors is probably associated with a certain psychosomatic pattern, but the difficulties of evaluating this in a large series of volunteer blood donors have thus far prevented any study of this possibility.

There have been approximately 34 donors who have exhibited symptoms and signs of shock sufficiently severe to require hospitalization for observation and, on a number of occasions, it has been deemed wise, in the judgment of the physician-in-charge at the Center, to autotransfuse donors who have had a severe reaction, in order to forestall the development of a more serious situation. All donors who have exhibited any reaction which would be classified as severe have been advised to make no further blood donations.

The widespread use of aromatic spirits of ammonia as a restorative in all Centers has required that special precautions be taken in its use. Six instances are reported in which the solution has inadvertently entered the donor's eye. Prompt washing out of the eye and the use of neutral ammonium tartrate (10%) alternating with 1% pantocaine prevented any serious damage.

The problem of syncope among blood donors is magnified by the accidents which may occur when syncope precedes or is accompanied by a fall. The accidents which have occurred under such circumstances are listed below:

(*a*) Scalp and head lacerations (108)
(*b*) Abrasions elsewhere (32)
(*c*) Basal skull fracture (2)
(*d*) Mandibular fracture (3)
(*e*) Fracture of nose (5)
(*f*) Fracture of malar bone (1)
(*g*) Fracture of finger (2)
(*h*) Fracture of clavicle (3)
(*i*) Fracture of olecranon process (1)
(*j*) Chipped teeth (18)
(*k*) Sprained ankle (4)
(*l*) Mild concussion (14)

Of all the complications which may occur coincident with or following a blood donation, cardiovascular accidents are the most disturbing. Individuals who present themselves for a blood donation, either as volunteers or professionals, are a selected group from two aspects. There is a high degree of self-selection in that the majority of these individuals know, or believe themselves to be, in reasonably good health. In addition, the history taken and the brief examination performed should eliminate all those who show any evidence of acute infection or of serious chronic disease, as well as those who by general health standards would be ineligible. It is undoubtedly true that the response of prospective donors to the questions asked may be inaccurate for a variety of reasons and it will be noted below that an evasive response on the part of the donor to the questions asked can assume major significance. Because the responsibility cannot be transferred, it has been the policy of the Service not to accept, on the basis of an outside physician's recommendation or request, any donor who does not meet the physical requirements as set up. This is of particular importance in the appraisal of donors with hypertensive cardiovascular disease.

No deaths attributable to cardiovascular causes have occurred in any Donor Center or at any Mobile Unit Station. The 10 deaths which have occurred within 48 hours of the donation are noted in detail in Table 2. It will be seen that in 5 of these cases a history of cardiovascular disease had existed but was denied by the donor at the time of examination. In all but 2 instances (Nos. 6 and 10), there was no indication before donation that the cardiovascular system might be suspect. Case 6 should not have been accepted as a donor on the basis of the predonation blood pressure; Case 10 was a 7-time donor;

TABLE 2.—FATAL CARDIOVASCULAR ACCIDENTS

Previ-	Findings before donation	Imme-

TABLE 2.—FATAL CARDIOVASCULAR ACCIDENTS

No.	Center	Date	Sex	Age	Previous donations	Findings before donation				Immediate reaction	Onset of symptoms	Outcome	Diagnosis	Remarks
						T.°	P.	B.P.	History					
1	A	4/21/43	M	50	1	98.4	78	160/90	Neg.	No	App. 6 hrs.	D. within 12 hrs.	Prob. coron. thromb.	
2	A	6/21/43	F	54	0	98.0	72	118/80	Neg.	No	App. 6–8 hrs.	D. ?	"	Made 100 mile trip home after donation; collapsed, died several hours later
3	B	7/43	F	44	2	98.6	80	120/70	Denied	No	4 hrs.	D. 12 hrs.	"	Family history of angina; donor had had previous attacks—denied history, later admitted by family
4	C	1/15/43	M	46	0	98.8	104	136/78	Neg.	Slight	4–5 hrs.	D. 5 hrs.	"	Autopsy diag.; coronary sclerosis and acute cardiac dilatation
5	D	8/25/43	M	46	0	98.2	84	134/80	Neg.	No	12 hrs.	D. 16 hrs.	"	
6	D	'43	M	48	1	98.0	86	202/128	Denied	No	48 hrs.	D. 48 hrs.	"	Previous history of "heart attacks" denied at time of examination
7	E	6/43	M	48	?	?	?	150/90	Denied	No	?	D. 48 hrs.	Cereb. hem.	History of treatment for hypertension obtained later
8	F	11/27/43	M	53	?	97.0	72	170/80	Denied	No	24 hrs.	D. 24 hrs.	Prob. coron. thromb.	Donor went bowling immediately after donation—had history of cardiac episodes, denied at time of examination
9	F	2/29/44	F	50	?	98.8	104 irreg.	140/80	Denied	Slight	3 hrs.	D. 72 hrs.	Cereb. hem.	History of treatment for hypertension; denied at time of examination
10	G	9/ 3/43	M	58	7	97.4	78	186/106	Neg.	No	Within 8 hrs.?	D. within 8 hrs.?	Prob. coron.	Not investigated

TABLE 3.—NON-FATAL CARDIOVASCULAR ACCIDENTS

No.	Center	Date	Sex	Age	Previous donations	Findings before donation				Immediate reaction	Onset of symptoms	Diagnosis	Outcome	Remarks
						T.°	P.	B.P.	History					
1	F	1/ 3/44	M	48	?	96.8	88	148/90	Neg.		During donation	Angina	Rec.	
2	H	12/13/43	M	47	1	98.8	110	148/90	Neg.	Slight	1 hr.	Left hemipl.	Rec.	
3	D	11/ 5/43	F	54	?	98.6	88	180/120	Denied	No	2 hrs.	Cereb. accid.	Rec.?	
4	D	2/19/42	F	57*	No	97.4	108	180/100	Denied	No	1 hr.	Card. failure	Rec.	Actual age not known—well over 60; hospitalized 2 weeks; hosp. diagnosis, "acute congestive heart failure"; history of chronic myocarditis
5	A	8/6/42	M	47	No	98.4	96	172/112	No		During donation	Cereb. accid. left hemipl.	Rec. (slow)	
6	A	5/42	M	63	No	98.6	88	150/106	Neg.		During donation	Coronary thrombosis	Rec.	Over age—accepted on recommendation of his own physician—such exceptions not permitted now.
7	A	3/25/43	M	46	?	97.8	92	160/100	Denied		During donation	Angina	Rec.	Had history of previous cardiac episodes; denied at time of examination
8	J	12/13/43	M	45	1	98.0	110	140/90	No	No	2 hrs.	Cereb. accid. left hemipl.	Rec.	

* Age given.

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exceptions have occasionally been made (for diastolic pressures over 100) in cases of this type.

Table 3 lists those cardiovascular accidents, occurring within 48 hours of the donation, in which the outcome was not fatal. It is entirely possible that an occasional unreported episode of this nature has occurred in addition to those noted. It will be seen that 4 of the 8 instances reported were cerebral accidents in contrast to the fatal group, in which only 2 of 10 were cerebral accidents. In addition, the onset of symptoms occurred during the bleeding in half of the non-fatal group, as contrasted with none in the fatal group.

In a group as large as that constituted by the donors (approximately 3,500,000 individuals) and encompassing the age distribution of such a group, a number of sudden deaths would be expected to occur within a period of 48 hours. It is, however, impossible to estimate how many might have occurred both because of the selection in the group and because detailed information is not available for this donor population on a number of other factors which influence mortality. However, on the basis of the nearest comparable standards derived from life insurance experience, the number of deaths that have been reported within 48 hours is considerably less than would be reasonably expected to occur, especially if it is taken into consideration that in 5 of the 10 deaths reported, the factor of selection did not operate because of incorrect answers to questioning.

Group 3. According to the card survey summarized in Table 4, approximately 4% of all individuals who donate blood experience some limitation of their activities during the week following the donation. There are, however, only rare instances reported of individuals who complained of weakness and lassitude for longer than 1 week. On thorough examination of most of these latter individuals it would appear that there was no physical basis for the persistence of symptoms and that these complaints were probably psychogenic in origin.

It has been the feeling of those closely connected with the medical aspects of the Service that the 4% of individuals noting prolonged lassitude following a donation consisted chiefly of those women who may not have regenerated their hemoglobin with normal rapidity. Until recently, a Tallqvist hemoglobin determination was made on all donors. Extensive investigative work[2] in several of the Centers revealed a fairly high percentage of error in the use of this method, especially in women whose hemoglobin was around the critical range of 80%. During the course of this work it was noted that a group of 220 women donors accepted for their first donation with a hemoglobin *over* 12.5 gm., determined by photo-electric cell colorimeter, did not show a diminution in their average hemoglobin at the time of their second or of their third donation. It may therefore be assumed that if an adequate hemoglobin level (accurately determined) exists at the time of the first donation, the problem of hemoglobin regeneration in women donors should be markedly lessened. As a result of this work, which will be reported shortly, the copper sulfate method of Phillips and Van Slyke[5] was instituted as a routine procedure for hemo-

* Age given.

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globin determinations in all Centers. It is hoped that the widespread use of this method will eliminate the majority of those whose acceptance was not warranted and who, as a result of donating 500 cc. of blood with a hemoglobin lower than the acceptable minimum, had

TABLE 4.—ANALYSIS OF INFORMATION RECEIVED

	Center A			Center B			Center C			Center D			Total		
Cards Given Out	9,665 - (Nov.-Feb.)			10,000 (Feb.-July)			10,000 (Dec.-March)			9,977 (April-July)			39,642		
Cards Returned	7,246 - (75.0%)			5,677 - (56.8%)			6,486 - (64.9%)			7,612 - (76.3%)			27,021 - (68.2%)		
	No. of Cards	Percent of: Total Returned	Percent of: Total Given Out	No. of Cards	Percent of: Total Returned	Percent of: Total Given Out	No. of Cards	Percent of: Total Returned	Percent of: Total Given Out	No. of Cards	Percent of: Total Returned	Percent of: Total Given Out	No. of Cards	Percent of: Total Returned	Percent of: Total Given Out
Cards on which no complaint was noted	6067	84.0	63.0	4472	78.8	44.7	5027	77.5	50.3	6463	84.9	64.8	22047	81.6	55.6
Cards registering any complaint or comment	1159	16.0	12.0	1205	21.2	12.1	1461	22.5	14.7	1149	15.1	11.5	4974	18.4	12.5
Analysis by type of complaint*															
Type 1 only	457	6.3	4.7	345	6.1	3.5	370	5.7	3.7	356	5.2	4.0	1567	5.8	4.0
" 2 only	454	6.3	4.7	480	8.5	4.8	432	6.7	4.3	480	6.3	4.8	1846	6.8	4.7
" 3 only	51	0.7	0.5	99	1.7	1.0	281	4.3	2.8	59	0.8	0.6	490	1.8	1.2
Types 1 and 2	87	1.2	0.9	131	2.3	1.3	140	2.2	1.4	105	1.4	1.1	463	1.7	1.2
" 1 and 3	60	0.8	0.6	59	1.0	0.6	40	0.6	0.4	39	0.5	0.4	198	0.7	0.5
" 2 and 3	28	0.4	0.3	48	0.8	0.5	125	1.9	1.3	40	0.5	0.4	241	0.9	0.6
" 1, 2 and 3	22	0.3	0.2	43	0.8	0.4	73	1.1	0.7	31	0.4	0.3	169	0.6	0.4
Totals for each type of complaint*	No. of Cards	Percent of: Total Complaints	Percent of: Cards Returned	No. of Cards	Percent of: Total Complaints	Percent of: Cards Returned	No. of Cards	Percent of: Total Complaints	Percent of: Cards Returned	No. of Cards	Percent of: Total Complaints	Percent of: Cards Returned	No. of Cards	Percent of: Total Complaints	Percent of: Cards Returned
Total complaints	1378	100.0		1529	100.0		1912	100.0		1396	100.0		6214	100.0	
Type 1	626	45.4	8.6	578	37.8	10.2	623	32.6	9.6	570	40.9	7.5	2397	38.6	8.9
" 2	591	42.9	8.2	702	45.9	12.4	770	40.3	11.9	656	47.0	8.6	2719	43.7	10.1
" 3	161	11.7	2.2	249	16.3	4.4	519	27.1	8.0	169	12.1	2.2	1068	17.7	4.1

* Key:
Type 1. Reaction immediately following donation.
Type 2. Slight to marked discomfort in the arm from which blood was taken.
Type 3. Some limitation of activity during week following donation.

justifiable reason for a complaint of prolonged lassitude and weakness.

It is of interest to note that the donation of 500 cc. of blood may have a variable effect on the menstrual cycle in women. There have been a few complaints of an excessive or prolonged period shortly following a donation; the majority of women who make any note of an irregularity report a delayed or scanty period. It has not been possible as yet to correlate this information with hemoglobin values existing at the time.

It has been a rule in the Blood Donor Service not to accept anyone as a donor who has had a history of malaria within the preceding 15 years, not because of the possibility of a transmission of the infection, as this has been shown to be most unlikely,[3] but because of the possibility of the reactivation of a long-dormant infection in the donor. In this connection an interesting example of a late or delayed reaction was found in a donor who, although he had had a history of malaria 7 years previously with subsequent relapses, answered in the negative when asked that question. After his second donation he called the Center and inquired as to why he had had chills and fever for several days following each donation. A further inquiry into his history was made, and the explanation for his "reaction" obtained; he was strongly advised to discontinue further donations.

Group 4. In a cross-section of the population as large and as varied as the donor group, it is obvious that certain situations will arise and certain accidents occur which will approximate the time of the blood donation, but will actually be coincidental and unrelated to the donation. These cases are of interest and concern to the Service chiefly because of the false rumors and misconceptions which they may initiate. As an example of this may be mentioned a female donor who complained of severe pain in the arm from which the blood was withdrawn shortly after the donation. A thorough examination of the donor, including Roentgen rays, at first revealed no basis for the complaint, although subsequent Roentgen rays some weeks later indicated an osteogenic sarcoma of the humerus. A similar coincidental relationship occurred in the case of a female donor who noted the onset of nausea, dizzy spells, and loss of memory shortly after a donation. A brain tumor was diagnosed shortly thereafter. Another donor died 48 hours after a blood donation, with a diagnosis of meningitis. As an example of a slightly different type of accident which may occur, the case history of one prospective donor is given below:

A female donor, age 24, reported at the Center for a blood donation at 1 P.M. on the appointed day. On examination prior to the donation, the following data were obtained: Temperature, 98.6°; pulse, 128; hemoglobin, 95%; blood pressure, 220/160. The history was otherwise negative. She was rejected because of the elevated blood pressure, and was preparing to leave the building when she complained of a pain in her head and fell to the floor with loss of consciousness. She struggled for a few seconds and then became moribund. The usual restorative measures were applied without success. Her family physician was notified and she was transferred by ambulance to a local hospital. She did not regain consciousness and died 9 hours after onset of symptoms.

Type 1. Reaction immediately following donation.
Type 2. Slight to marked discomfort in the arm from which blood was taken.
Type 3. Some limitation of activity during week following donation.

This is the only incident of this type which has occurred. It is of importance not only because of the implications and repercussions which would have developed had this donor been bled, but also because of the fact that the incident serves to emphasize the necessity for a strict observance of the eligibility regulations for blood donors, especially as regards any history of and/or signs of cardiovascular disease.

Two cases are reported in which donors were said to have developed leukemia within 3 months of the donation. In both cases, examination of the donor was entirely negative at the time of the donation, and the development of that particular disease process can only be considered coincidental.

FIG. 2.—CARD REQUESTING INFORMATION

Date_____ M.____ F.____ Age____ No.____

You have generously donated your blood to the Armed Services. Will you kindly fill out and mail this card one week from the date of your donation?

(1) Did you have any ill effects immediately after donating your blood?_____

(2) Was the arm from which the blood was withdrawn sore, stiff, or markedly discolored?_____

(3) Were you in any way limited in your activity during the week after you donated blood?_____

(4) Remarks_____

No Signature Needed

It is the customary procedure in all Centers to note on the donor's medical card whether or not that donor had a reaction at the time of the donation. It is ordinarily impossible, however, to obtain any accurate estimate of the donor's own reaction to the procedure, both as to any prolonged after-effects and as to the complications related to the mechanical procedure of withdrawal of the blood. To obtain such information, a card (Fig. 2) was given to 10,000 consecutive donors in each of four fixed Centers in various sections of the country. The donor was asked to mail the card back to the Center 1 week after the donation. The results are tabulated in Table 4.

It will be noted that out of 39,642 cards given out, 68.2% were returned. In analyzing the figures, it will be seen that the percentage of cards with complaints or comment in relation to the total returned is highest where the percentage of returned cards is the lowest. In relation to the cards given out, the percentage of cards with complaints or comments is much more uniform. It is a safe assumption, therefore, that the percentage with complaints among those not returning the cards is distinctly lower than among those returning the cards.

No attempt was made to separate the complaints on the basis of severity. The donor was permitted to make his own estimate of his reaction, and all complaints or comments noted were included in the final count, although many were obviously negligible. On this basis,

it will be noted that 8.9% of those who returned the cards noted some reaction immediately following the donation; 10.1% noted varying degrees of discomfort of discoloration in the arm from which the blood was taken; and 4.1% noted some limitation of their activities within the week following the donation.

Anyone who has had wide experience in hospital or private practice is well aware of the forms which "hysteria" may take, especially in individuals with hypochondriac tendencies. It might, therefore, be expected that in a project with such a high degree of emotional appeal, there might be many individuals who would attempt to attach a multitude of minor complaints to the fact that they had given a blood donation. Whether because of the high degree of self-selection automatically practiced by the donors or whether because of the coöperative impulse involved in donating blood, there have been few instances in which a justifiable reason has not existed for a donor's complaint.

Summary. 1. With a controlled basis of operations for all procedures and a rigid eligibility standard for all donors, the withdrawal of 500 cc. of blood from normally healthy individuals should offer no serious potential hazard to the donors. The experience of the American Red Cross Blood Donor Service to date has confirmed this assumption.

2. Approximately 10% of the 40,000 donors studied have (for technical reasons) experienced transient discomfort in the arm from which the blood was withdrawn.

3. Approximately 9% have experienced some form of a transient reaction during or immediately following the donation. This number is fairly constant in a general cross-section of the population in the age group selected, and is dependent on a variety of factors which are not constant. The instances of delayed reactions or syncope occurring some hours after the donation are rare. The symptoms encountered in order of frequency are listed.

4. The cardiovascular complications which have occurred are reported, but in view of the fact that the normal expectancy for accidents of this nature is far greater than the actual experience of the Service, regardless of whether or not the factor of selection is considered, it is impossible to conclude that these complications were directly related to the withdrawal of blood.

5. A certain number of individuals, approximately 4%, have experienced prolonged or late manifestations, the basis for which may have been a delayed regeneration of hemoglobin. Only a very small group has developed symptoms for which there is no apparent physical basis.

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THE USE OF A "MODIFIED GLOBIN" FROM HUMAN ERYTHROCYTES AS A PLASMA SUBSTITUTE*

PRELIMINARY REPORT

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BLOOD is a very complex substance with numerous physiologic attributes. The thought of fractionating human blood and of using the various components for the purpose best suited appears natural and presumably occurred to many before our work was begun. In a letter of Captain Ward at the close of the last World War, plasma was suggested as a therapeutic means in the treatment of shock. Robertson actually used preserved red cells for the treatment of shock.

The practical application of fractionation of human blood to therapeutics does not appear to have gone any further before 1927. In that year we began fractionation of citrated blood by centrifugation. By this simple means blood can be divided into three portions: (1) Supernatant layer containing plasma and a portion of the platelets; (2) a buffy coat or leukocytic cream containing the bulk of the leukocytes and platelets; (3) a layer of underlying erythrocytes.

These three portions were administered from that time on to patients, and it soon became evident that the idea of blood fractionation suggested by *a priori* considerations was sound, practical and yielded good results. Although of these three portions plasma was used more extensively, the first outstanding results were obtained with the use of leukocytic cream, a fraction which has not received lately the attention that it deserves. The use of *citrated plasma* need not be discussed here.

The "*leukocytic cream*" has been suggested[27] as an effective bone

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marrow stimulant in all cases of agranulocytosis not due to a severe myelophthisic or aplastic lesion. With the cases included in the first publication, a total of at least 26 cases of severe neutropenia (agranulocytosis) have been treated so far. Of these, 23 recovered and 3 died. All the fatal cases showed at autopsy a very severe hypoplasia of the bone marrow, a condition not generally present in agranulocytosis.[7] The predominant lesion in agranulocytosis is a defect in the mechanism of maturation of the granulocytic cells.

The *erythrocytes*, resuspended in salt solution, have been used occasionally by us and others in the treatment of acute and chronic anemias, usually of the posthemorrhagic type. More recently, with the large amounts of red cell residue left from the preparation of plasma for the Armed Forces, utilization of red cells for transfusion[1a–j] and for surgical dressing[14a,b] has been emphasized. Presumably, with the finding of better methods of erythrocyte preservation than now available, suspension of erythrocytes left over from plasma preparation will find a definite place as a therapeutic agent. While, therefore, this work should continue, there are at present several limitations to a generalized use of red cell residue from plasma preparation. Some of the most important are: (1) In the majority of hospitals, plasma is prepared from blood which has been kept in the refrigerator to the limit of safe erythrocyte preservation. (2) When the red cells are the by-product of commercial plasma preparation, the area of distribution is naturally limited. (3) The safe limit of preservation of centrifuged resuspended cells is short. (4) Not all anemic patients are adequately treated with erythrocytes alone.

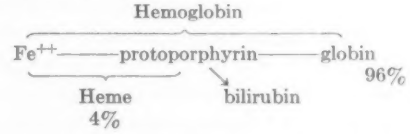
In addition to the unusually large amount of red cells now available from plasma preparation for the Armed Forces, there will always be the opportunity of utilization of large quantities of red cells which remain from the routine preparation of plasma in many hospitals throughout the country or from state wide organizations.

In this preliminary paper, evidence will be presented that a globin can be prepared from human erythrocytes which is safe and which has a wide field of application as a plasma substitute in the human. It is recognized that the expression "plasma substitute" is very confusing, there being no substance which has the same physicochemical and physiologic attributes of plasma. However, the term has been so widely used that one must accept it. It is used here in a limited sense to indicate a substance possessing some of the properties of plasma: more specifically, a high colloidal osmotic pressure. Because of this property and of other physicochemical properties, globin solutions can be successfully used to replace lost blood volume.

Outline of Composition of Hemoglobin. The hemoglobin content of normal human blood varies, but it is usually 14 to 16 gm. per 100 cc. Hemoglobin is very soluble in water, and consists of 3 components: iron, porphyrin and a protein, globin. Globin constitutes about 96% of the total hemoglobin. The structure of the porphyrin nucleus is fairly well known chemically. It consists of four pyrrole rings connected cyclically through carbon atoms.

There is some confusion in nomenclature, but the alkaline iron-porphyrin compound is usually known as alkali hematin or heme, while the acid hematin is known as acid heme.

When hemoglobin is broken down in the body, the 3 components are apparently split from each other. The iron is retained by the body for the formation of new hemoglobin. Some or all of the porphyrin, which has been identified as protoporphyrin, is converted to bilirubin. It may be assumed that the fate of the globin is similar to that of any other native tissue protein. The 3 components of hemoglobin can be separated chemically with relative ease. Mild treatment of oxyhemoglobin with acid readily cleaves the globin from the iron-porphyrin combination. Treating oxidized heme with a weak acid will give iron plus protoporphyrin.



Preparation and Properties of Globins. In 1871 Preyer[16] demonstrated that hemoglobin could be split into its two components of hematin and globin by treatment with a strong acid. This method of preparing relatively pure globin was used in 1898 by Schulz,[24] who pointed out that in the preparation of globin, the concentration of the acid used for the decomposition of hemoglobin was of primary importance. The final globin product was soluble in either dilute acids or alkalies but insoluble at its iso-electric point, which according to Osato[15] was at a slightly alkaline pH. The lethal dose of this globin to rabbits according to Schittenhelm[23] was 0.15 gm. In 1913 Robertson,[18] using essentially the methods of Schulz but with some small modifications, obtained 3 fractions of globin.

Other workers, notably Bertin-Sans and Mortissier,[5] Anson and Mirsky[3] and Barcroft,[4] using slight modifications of Schulz's procedure for the production of globin, showed that they were able to resynthesize hemoglobin from the two products of hemoglobin cleavage. If this was so, then the globin obtained by them was probably not a denatured product as obtained by Schulz. Hill and Holden[12] stated that the globin as prepared by the Schulz method was a type of metaprotein such as is normally obtained when dilute acids acted upon albumins or globulins. These workers claimed to have obtained an undenatured globin by using a minimum quantity of acid to split the hemoglobin and by carrying out all procedures at 0° C. Haurowitz[11] has classified this globin as an albumose while Schenck[22] classed it as a transitional substance falling somewhere between basic peptone and histone.

Anson and Mirsky[2] incorporated the use of an organic solvent with acid for the preparation of globin. Hydrochloric acid solution in acetone was used for splitting hemoglobin. Roche[19] had found that at least 3 different globins were formed when hemoglobin was treated with acids, namely, native globin, fully denatured globin and an

intermediate substance insoluble at the iso-electric point which has been termed "paraglobin."

In this same period, Schenck[22] also outlined a method for globin preparation employing an acid acetone. The lethal dose of this globin in a 2.5 kg. rabbit was 0.75 gm., while doses up to 0.4 gm. were well tolerated.

Roche *et al.*[21] in 1932, working with globins prepared by the method of Hansik[10] and also of Anson and Mirsky, studied their stability and osmotic pressures. Their observations indicated that native globin was fairly stable, although the globin prepared by the method of Anson and Mirsky was relatively unstable even when kept at 0° C. Reiner *et al.*[17] found that the globin prepared by the method of Anson and Mirsky when analyzed electrophoretically consisted of 2 components: a "slow" component approximating about 40% of the material and a "fast" component consisting of approximately 60% of the material. A small fraction of purified globin prepared by 55% saturation with $(NH_4)_2SO_4$ as proposed by Roche and Combette,[20] showed the same pattern after 2 weeks of continuous dialysis.

Gralen,[9] using the method of Anson and Mirsky for the preparation of soluble globin, found that the solutions obtained were never very stable. This observation was also made by Roche *et al.*[21] The molecular weight by Svedberg's formula was found to be 37,000 for globin. The latter is similar to that obtained by Steinhardt[26] for the urea-hemoglobin solution.

The molecular weight of globin as determined by Svedberg[25] was of an indeterminate nature consisting of high molecular weight material ranging down to 17,000. He characterized hemoglobin as consisting of 4 globin units of 17,000 molecular weight each.

Roche *et al.*[21] stated that the molecular weight of globin obtained osmometrically depended on the concentration of the protein solution being analyzed. It was possible at times to obtain a molecular weight for globin which was greater than that of hemoglobin.

Summary of Literature. A review of the literature indicates that a number of widely different "globins" can be obtained, according to the method of preparation, and that little, if any, pure "native" globin can be obtained with any of the methods proposed. The products so far obtained fall into three categories: (1) The denatured globin of Schulz, soluble in dilute acids and alkalies. Upon reconstitution with alkaline hematin it gives rise to a hemochromogen instead of methemoglobin. This material has been found to be toxic in relatively small doses when inoculated into rabbits. (2) The globin as prepared by Hill and Holden. This material, prepared at 0° C. without the use of alcohol, was found to be soluble over a pH range of 5 to 10 and appeared relatively stable. Upon resynthesis with alkaline hematin the characteristic band of hemoglobin was obtained. No toxicity studies were made with this globin. (3) The acid-acetone globin of Anson and Mirsky. This material has been the most widely studied. By means of this method of preparation, 3 distinct types of globin are obtained: (*a*) "native globin," (*b*) denatured globin, and (*c*) "paraglobin."

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In the purification process employed paraglobin was eliminated, leaving essentially a soluble globin. This material upon recombination with alkaline hematin has given the characteristic band of methemoglobin. It must be remembered that even small amounts of native globin would give the hemoglobin band so that this method of identifying globin is not satisfactory. This was substantiated by Gralen.[9] Stability studies indicated that this globin underwent chemical changes when kept either as a dried powder or as an aqueous solution.

We have found that this globin was toxic to rabbits. Electrophoretic studies indicated that this globin consisted of 2 portions: 40% of a slow component and 60% of a fast component.

General Properties of "Modified Globin" so far Determined. As yet, not all the properties of "modified globin" have been fully investigated. The following general attributes are listed at this time: (1) It is soluble in water at pH 7.4 to give at least a 25% solution. (2) It possesses a minimum solubility at about pH 6.5. (3) The viscosity is appreciably lower than that of citrated plasma. (4) The molecular weight of 85% or more of the modified globin as determined by ultracentrifugal studies by Cohn and Oncley[6] is around 34,000. This percentage varies to a certain extent with the process of modification. (5) Preliminary studies indicate that the molecule is quite symmetrical. (6) The approximate yield is about 250 gm. for each 1000 cc. of packed erythrocytes. (7) Preliminary observations indicate that solutions in 0.85% saline solution are stable under ordinary conditions of preservation. (8) Solutions are miscible in all proportions without precipitation, clumping or hemolysis with citrated human plasma and blood. (9) Solutions in saline do not increase the rate of sedimentation of erythrocytes when added either *in vitro* or *in vivo* to whole blood. (10) The intravenous injection of sufficiently large quantities of "modified globin" in normal or hypoproteinemic humans produces an hemodilution lasting, in the majority of cases, 24 to 120 hours.

Toxicity and Antigenic Properties. Globin solutions injected intravenously in rabbits and intraperitoneally in guinea-pigs and mice have been found to be non-toxic. Repeated intravenous administrations of globin to rabbits over a period of several months have not given rise to reactions nor to signs of antibodies formation as determined by precipitin tests. Johnson and Bradley[13] had likewise found that a human globin was non-antigenic when injected into rabbits, although globin similarly prepared from other animal species proved to be antigenic. Weekly injections of globin subcutaneously to small guinea-pigs for periods up to 8 weeks have shown no anaphylactogenic properties. In these experiments the globin was *not* alum precipitated.

In the human, skin tests in over 100 patients belonging to all blood groups have shown no positive reactions. Patients receiving large doses of globin intravenously over long periods of time have shown no late untowards reactions.

So far, a total of 210 intravenous injections of globin have been administered to 108 humans. The total amount of globin thus administered is 3734 gm. The largest single dose has been 57 gm., the largest amount to 1 patient in 24 hours 60 gm. One patient received

92 gm. in 36 hours. The largest total amount administered to any one patient has been 192 gm.

Several patients have received repeated injections of globin over long periods of time. All these patients showed no reaction to any injection and repeated skin tests yielded a negative result.

The concentration of the globin administered intravenously to humans has varied from 1.8 to 6.8%.

A few pyrogenic reactions which occurred in the beginning were readily eliminated by instituting the usual biologic controls. The use of modified globin prepared by the standard method has given rise to no severe reactions nor any delayed untowards effect.

Solutions of some globins have shown in some persons a pressor effect and solutions of other globins a vasomotor effect. None of these reactions could be considered as severe; but they can be largely eliminated by proper technique in the preparation of the globin and subsequent purification.

Globins containing large molecular aggregates, soluble in alkaline pH range only, have given rise, when injected intravenously in experimental animals, to embolic lesions, with immediate death or severe organic damage. In the method of preparation followed for modified globin used in humans, the material unstable at pH around 7.4 has been carefully eliminated.

Use of Modified Globin in the Treatment of Secondary Shock. Up to the present time 15 patients suffering from secondary shock have been treated with globin solutions. Two have received inadequate amounts of globin and 13 have received sufficient amounts of globin to combat the shock. All of these patients are considered as having responded satisfactorily to the treatment.

These patients may be divided as follows:

1. Shock as a result of hemorrhage and tissue destruction from bullet wound	2
2. First, second and third degree burns involving one-half of body surface	1
3. Shock from hemorrhage from stab wounds	2
4. Hemothorax and cerebral hemorrhage as a result of automobile accident	1
5. Postoperative shock	9

They will be reported separately in detail.

Comments. The expression "plasma substitute" used in this paper is not to be construed as meaning that globin solutions can replace plasma in all instances. At best, "modified globin" solutions can be expected to replace plasma insofar as colloidal osmotic properties are concerned.

It is estimated that every year nearly 1½ billion cc. of packed red cells may be made available from the preparation of plasma for the Armed Forces and for the civilian population. By a relatively simple process, this hemoglobin can be transformed into a "modified globin" at a fraction of the cost of plasma production.

From the amount of red cells mentioned above 375,000 kg. of globin can be prepared, with an osmotic power about twice as great as an equivalent amount of plasma proteins, that is, an osmotic equivalent of about 12½ million liters of citrated plasma. In other words, from a blood donation it is possible to obtain about 250 cc. of plasma (about

17 gm. of plasma proteins) and about 24 gm. of globin. This globin is equivalent in osmotic power to about 600 cc. of plasma. Thus from a single 500 cc. donation of blood it is possible to obtain the osmotic equivalent of about 4 donations.

As yet, the properties of this modified globin have not been fully investigated. It has been ascertained that this material is: (1) safe; (2) capable of replacing lost blood volume in cases of severe secondary shock.

These results justify a full-scale investigation to determine more completely the physicochemical, physiologic and pharmacologic properties of this modified globin.

Conclusions. A "modified globin" can be prepared from human erythrocytes left over from plasma preparation. This globin is safe and has been satisfactorily used as a plasma substitute to restore lost blood volume in human patients suffering from secondary shock.

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HEMOPHILIA-LIKE DISEASE IN THE FEMALE

WITH A NOTE ON THE CLOTTING TIME OF THE RECALCIFIED PLASMA

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BY definition hemophilia is a bleeding disease manifesting itself early in life, occurring only in the male but being inherited through the female. The question whether the characteristic active defect of hemophilia can occur in women has not been satisfactorily answered. A number of cases have been reported which closely approximate the clinical picture of hemophilia and have the characteristic delay in coagulation time without other demonstrable hemostatic defects. Until recently, however, the diagnosis of hemophilia has been uncertain and subject to serious error; consequently all cases which have not conformed to the classical definition must be viewed with reservation. It is felt that the following case may shed further light on the group of hemophilia-like diseases occurring in the female.

Case History. Mrs. H. B., age 30, housewife, was first seen in February 1943 in consultation with Dr. P. Currer. Her father had died at the age of 57 with carcinoma of the rectum and her mother had died at 33 with pneumonia. Three brothers and 1 sister were living and well and no siblings had died. There was no known instance in the family for 3 generations of abnormal tendency to bleed or to bruise easily. The past medical history was entirely negative except for repeated attacks of tonsillitis before the age of 10, otitis media at the age of 4 and a small duodenal ulcer at the age of 19 which healed promptly with dietary control. She had had 3 normal pregnancies, all of which had been terminated by Cæsarean section; the last one in December 1941 without unusual bleeding. Menstrual flow since the last pregnancy had been somewhat greater than previously but had never required more than 5 to 6 pads daily for 3 to 5 days. In April 1942 there had been a rash around the waist which was thought to be "shingles." In May 1942 she noted for the first time a sudden sharp unexplained pain deep in the left calf muscles which was followed with moderate swelling, pain and, in 36 to 48 hours, extensive ecchymosis. This experience was repeated in the arm in a few days and subsequently in multiple areas, many of which showed only moderate swelling and ecchymosis. In no instance was trauma responsible for the sudden hemorrhage—in fact, the patient recalled a severe fall on her knee without bruising. She had 2 severe episodes of hematuria—the first attack lasted 3 weeks while the latter subsided in 4 days but was very severe and was accompanied by pain over both renal areas. The characteristic deep muscular and subcutaneous hemorrhages continued until in October 1942, when the gums bled for a short period and the deep hemorrhages seemed to increase in size and frequency to the time of observation. At that time (February 1943) hemorrhages were of sufficient extent to incapacitate the patient for a few days and to cause very severe pain.

Physical examination was entirely negative except for marked swelling and

tenderness of the left forearm from the wrist to the elbow and variably sized ecchymotic areas over the other extremities. Laboratory findings were:

Hemoglobin	13 gm.
R.B.C.	3,970,000 (mild normochromic anemia)
W.B.C.	8650 (normal differential count)
Platelets	316,000 (normal)
Sedimentation rate	30 mm. in 1 hour
Plasma ascorbic acid	0.5 mg.
Tourniquet test	Moderately positive (25 petechiæ in 2.5 cm. circle)
Coagulation time (Lee-White method)	17 minutes (delayed)
Coagulation time of recalcified plasma	5 minutes (normal)
Clot retraction complete in	40 minutes (normal)
Bleeding time	2 minutes (normal)
Prothrombin concentration	100%

She was given large amounts of fruit juices, cevitamic acid and subsequently hesperidin without appreciable effect on the tourniquet test. The muscular and subcutaneous hemorrhages continued with variable frequency. On March 4, 1943 hemorrhagic study showed:

Clotting time (Lee-White method)	19 minutes
Clotting time of recalcified plasma:	
After high centrifugation	6 minutes 15 seconds
After low centrifugation	5 minutes 30 seconds
Prothrombin concentration	100%
Platelets	260,000 (normal)
Tourniquet test	2+
Hemoglobin	12.5 gm.
R.B.C.	3,840,000
W.B.C.	6450

A period of apparent improvement followed and on April 21, 1943 the tourniquet test was normal and the blood count was within normal limits. Suddenly during the night of April 25 spontaneous hemorrhage appeared in the base of the tongue and the mucosa of the pharynx causing difficulty in breathing and swallowing. Hemorrhagic study on hospital admission showed:

Coagulation time (Lee-White)	21 minutes
Bleeding time	2½ to 4¾ minutes (normal)
Clot retraction	95 minutes (normal)
Prothrombin	90 per cent
Platelets	290,000

The clinical course seemed satisfactory for 36 hours when complete respiratory obstruction occurred very suddenly. Tracheotomy was done immediately but in spite of oxygen and artificial respiration, the patient failed to respond.

The *autopsy* findings were completely negative except for the extensive hemorrhagic infiltration of the sublingual, submaxillary and laryngeal areas and slight tubular degeneration of the kidneys.

Discussion. It is obvious that this case resembles hemophilia both clinically and in the laboratory findings. The bleeding into the muscles, intermittent hematuria and the final hemorrhage into the base of the tongue observed in this case are common forms of bleeding in hemophilia.

As in hemophilia, the patient's bleeding time, clot retraction time, prothrombin concentration and platelet count were normal, whereas the coagulation time was distinctly delayed. There were, however, striking differences between the hemorrhagic diathesis of our patient and true hemophilia. The latter disease appears early in childhood, occurs

exceedingly infrequently if ever spontaneously in adults, and has the well-known characteristic hereditary pattern.

The laboratory findings are similar in both this hemophilia-like condition and the true hereditary disease except for one test—the clotting time of recalcified plasma. Oxalated hemophilic plasma subjected to high centrifugation clots significantly slower on recalcification than that obtained by spontaneous sedimentation or slow centrifugation. In marked contrast the plasma of this patient failed to show this striking difference due to centrifugation. The significance of this test is not yet known, but one of us has observed that the test has been consistently positive in a small series of hemophilia cases[4] and that it was negative in one other atypical or hemophilia-like condition.

The relationship of this diathesis to the other hemorrhagic diseases presents an interesting and important problem. According to the commonly accepted classification, the true bleeding diseases can be divided into two primary groups: one in which the hemostatic defect is vascular, the other in which a disturbance of the coagulation mechanism occurs. In the first class the coagulation is normal while in the second class it is delayed or absent. Coagulation of the blood depends on 3 factors: fibrinogen, prothrombin and thromboplastin; therefore, diminution or absence of any one of these agents in the blood causes a retardation of clotting. It is now well recognized that fibrinogen and prothrombin are not diminished in hemophilia, but with the less critical diagnostic methods of the past it is probable that cases of hypofibrinogenemia were erroneously called hemophilia. Hypoprothrombinemia, especially the idiopathic type, likewise has been mistaken for hemophilia. The case of Rhoads and Fitz-Hugh[6] was regarded as hemophilia for 9 years before the low prothrombin of the blood was discovered. Since the clinical picture of idiopathic hypoprothrombinemia closely resembles that of hemophilia, one must conclude that at least some of the cases of atypical hemophilia recorded in the literature were in reality hypoprothrombinemias. Unfortunately all these cases are valueless unless restudied with the newer methods, for it is impossible to arrive at an unequivocal diagnosis on the basis of the data consisting of the clinical history and the coagulation time.

It is evident that hemorrhagic conditions exist which, like hemophilia, lack available thromboplastin, or to state it in an entirely noncontroversial manner, in which the prothrombin is activated too slowly to meet the hemostatic demands. In this group can be included the newly discovered hemorrhagic disease of swine.[3] Curiously this disease is transmitted by and occurs in both sexes. Except for this it closely resembles human hemophilia. The coagulation time of recalcified oxalated plasma is influenced markedly by centrifugation just as in true hemophilia.

Our case demonstrates that a hemophilic-like diathesis which is not hemophilia can occur in women. In 1938 Joules and Macfarlane[1] described a similar case of a woman aged 56 who, following an extraction of a tooth, developed a hemorrhagic diathesis—hematuria, rectal bleeding, hemorrhage into tissues such as her tongue and joints.

The family history was entirely negative in regard to hemorrhagic diseases. Interestingly, the blood when mixed with Russell viper venom (a thromboplastic-like agent) clotted nearly as fast as normal blood, thus behaving similar to hemophilic blood. The clotting times (with venom) of their patient, of a normal and of a hemophilic subject were 31, 17 and 23 seconds respectively. The Lee-White coagulation time of the patient ranged from 43 to 67 minutes. Obviously the defect in coagulation was in the availability of thromboplastin, and therefore this case is identical or closely related to ours.

Recently Dr. Albert Loveman[2] informed us of a case closely simulating the one we have described. His patient, a woman aged 33, developed a hemorrhagic diathesis a year after the birth of a child. The hemorrhages were mostly superficial—subcutaneous rather than intramuscular—with spells of epistaxis and one attack of hematuria. The prothrombin was 88% of normal and the Lee-White coagulation test 1 hour and 50 minutes. The family history was negative.

These 3 cases appear to be essentially identical. In each the hemorrhagic condition appeared in an adult female who had had no previous attacks of abnormal bleeding nor any history of hemorrhage in the family. The clinical picture and the type of bleeding simulates hemophilia, and is almost certainly due to the prolonged coagulation time of the blood. The diathesis can be equally as serious as hemophilia and may terminate fatally as illustrated by our patient. In the case of Dr. Loveman as well as in ours, the hemorrhagic condition began several months after the birth of a child. Whether this was merely incidental is difficult to say. Significantly in both patients menstruation was normal and unaccompanied by excessive bleeding in spite of a prolonged coagulation time which seems to indicate that the hemostatic control of menstrual bleeding is not dependent upon the coagulation mechanism.

TABLE 1.—DIFFERENTIAL DIAGNOSIS OF HEMOPHILIA AND HEMOPHILIA-LIKE DISEASES

	Human hemophilia	Swine hemophilia	Hemophilia-like disease in women
Heredity	Recessive sex-linked	Simple recessive	
Sex appears in	Male	Male and female	Female*
Transmission by	Female	Male and female	
Time of onset	Infancy	Early	Adult life
Bleeding: Type	Deep	Deep	Deep
Cause	Traumatic	Traumatic	Spontaneous
Coagulation	Delayed	Delayed	Delayed
Clotting time test of recalcified plasma	Positive	Positive	Negative

It is interesting to speculate as to the rôle of the vascular dysfunction in the bleeding of our patient. The tourniquet test was positive on

* The authors have been informed by Dr. B. E. Hall that he has studied a male patient at the Mayo Clinic who presented a clinical picture similar to the case described in this paper. The patient had a negative family history concerning bleeding diseases, and he showed no hemorrhagic tendency until at the age of 52 years. He had rectal bleeding and several ecchymoses. There was also marked swelling and limitation of motion of the left knee. Laboratory findings were normal except for a delay of the coagulation time of the blood (40, 36 and 55 minutes).

several occasions and the hemorrhages occurred without any demonstrable preceding trauma. These findings are characteristically present in purpura and not in hemophilia. It would seem justifiable to regard the vascular changes in this instance as coincidental rather than as secondary or related to the coagulation defect and of clinical importance only in relation to the spontaneous nature of the bleeding. The coagulation defect appears to be the primary factor and it seems appropriate that the term "hemophiloid" be considered in describing such a diathesis as one of us has previously suggested.[5]

The principal differences between this clinical entity, true hemophilia, and the hemophilia-like disease of swine are summarized in Table 1.

Treatment is as unsatisfactory as in hemophilia. Transfusion must be looked upon as a makeshift therapy, but as the best so far known. In view of the fact that after numerous studies divergent theories are still held concerning the fundamental defect in hemophilia, it seems unwise to attempt an explanation of the coagulation disturbance in this new entity. Only as theoretical studies advance knowledge concerning the fundamentals of coagulation can a solution of hemophilia and allied conditions be expected.

Summary. A study is presented of a female patient with a hemorrhagic disease that closely simulates hemophilia. The disease is discussed and its similarity to and its differences from true hemophilia are considered.

The diagnostic value of the clotting time test of recalcified plasma is pointed out.

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CARDIAC HYPERTROPHY AND EXTRAMEDULLARY ERYTHROPOIESIS IN NEWBORN INFANTS OF PREDIABETIC MOTHERS

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Recent studies have shown that striking changes frequently occur in many of the tissues of infants born to diabetic mothers. In addition to the increased body weight and hyperplasia of the islands of Langerhans, which have been recognized for many years, it has been demonstrated that these infants sometimes have at birth cardiac hypertrophy and extramedullary erythropoiesis,[8] adrenal hyperplasia,[7] an increased

eosinophilia of the anterior hypophysis[1,4,9] and hyperplasia of the genital organs in the female.[2,10] In the course of their study of infants born to diabetic mothers, Miller and Wilson observed that many of the above changes were present in 2 infants born before signs or symptoms of diabetes appeared in their mothers.[8] Similar observations were made in 2 other infants by Miller, Johnson and Durlacher[7] and in a fifth infant by Miller, Hurwitz and Kuder.[6] The diagnosis of this syndrome in infants born to mothers who have not yet developed diabetes is of importance to the clinician not only in directing the care of the infant in the neonatal period but also in anticipating the onset of diabetes in the mother. In order to make it possible for more infants with this symptom to be recognized, the relevant clinical and autopsy findings in the 5 infants mentioned above and the case histories of 2 other infants, who survived, are brought together in this report.

TABLE 1.—SIGNIFICANT CLINICAL DATA ON PREGNANCIES OF 7 MOTHERS WHO LATER DEVELOPED DIABETES

Case	Present pregnancy				Diabetes				Kahn	Rh
	Gravida	Age	Glycosuria	Blood sugar (mg. %) (fasting)	Time of onset after pres. preg.	Character of onset	Regulated by	Period of diabetic follow-up		
1[1]	2	22	0, day before and day of delivery	68, day of del.	4 mos.	Gradual	Insulin	7 mos.	Neg.	
2[1]	8	43	0, 3 and 8 days postpartum	75, day of del.	1½ yrs.	Gradual	Diet	6 mos.	Neg.	
3[3]	2	24	0, 5 months antepartum	.....	9 mos.	Gradual	Insulin	15 mos.	Neg.	Neg.
4[3]	5	38	0 to 4+, for 2 mos. antepartum	116, 96 and 117, last trimester	6 mos.	Gradual	Insulin	9 mos.	Neg.	Pos.
5[2]	6	30	0, postpartum	.....	5 yrs.	Gradual	Diet	3 mos.	Neg.	
6*	12	38	0, 1 day postpartum	.....	2 yrs.	Gradual	Diet	3 yrs.	Neg.	Pos.
7*	4	36	0, 4 mos., 1 mo. and 9 days antepartum	.....	2 days	Sudden with acidosis	Insulin	9 yrs.	Neg.	

* See Case Reports 1 and 2.

The significant clinical facts on the 7 mothers are summarized in Table 1. They were multiparas whose ages ranged from 22 to 43 years at the time of the births of the infants reported in this study. The Kahn tests on the mothers' bloods were negative. Rh determinations were made in 3 mothers: 2 were Rh positive (Cases 4 and 6) and 1 was Rh negative (Case 3). No evidence of glycosuria was found in any of the mothers except 1 (Case 4), and in this instance reducing substances in the urine were found on several occasions in the last 2 months of pregnancy. However, the fasting blood sugar concentrations in this mother were not over 117 mg. per 100 cc. on 3 separate occasions during the period glycosuria was present. Two other mothers (Cases 1 and 2) had normal fasting blood sugar concentrations on the day of delivery. None of the 7 mothers had any symptoms of diabetes before or during the pregnancies under discussion. Signs and

symptoms of diabetes developed in the mothers from 2 days to 5 years following the births of these 7 infants. In all but 1 mother (Case 7) the onset of diabetes was gradual. In Case 7 there was a sudden onset of diabetic acidosis 2 days postpartum, associated with a respiratory infection and pyelitis. During the time they were under observation for their diabetes 4 of the mothers required insulin (Cases 1, 3, 4 and 7), while in the remaining mothers the diabetes was regulated solely by diet.

TABLE 2.—SIGNIFICANT AUTOPSY FINDINGS IN 5 INFANTS WHOSE MOTHERS LATER DEVELOPED DIABETES

Case*	Day of death	Birth wt. (kg.)	Heart wt. (gm.)	Extramedullary erythropoiesis	Hyperplasia islands Langerhans	Adrenals wt. (gm.)	Anterior hypophysis
1	Stillborn	5.9	29	Liver			
2	Stillborn	5.5	65	...	++		
3	2	4.4	50	Liver, spleen heart	++++	17	Eosinophilia increased
4	3	2.6	Large by Roentgen ray	Liver			
5	3	4.1	36	Liver and stomach	...	14	

* Case numbers in this table correspond to case numbers in Table 1. Cases 6 and 7 of Table 1 survived.

The postmortem findings on the 5 infants who died are summarized in Table 2. The data on several of the infants are incomplete because records of the examination of some of the viscera were omitted from the autopsy protocols. Cardiac hypertrophy, as judged by the data on normal heart weight of newborn infants compiled by Miller,[5] was marked in Cases 2, 3 and 5. The heart was not weighed in Case 4, but it was found to be enlarged on Roentgen examination before death and the muscle fibers were described as hypertrophied in the autopsy protocol. There was an excessive amount of erythropoietic tissue in the livers of the 4 infants examined for this change (Cases 1, 3, 4 and 5), and additional evidence of abnormal erythropoiesis was found in the spleen and heart of Case 3 and in the stomach of Case 5. Hyperplasia of the islands of Langerhans was observed in Cases 2 and 3, the only 2 infants examined for this change. Assuming that 10 gm. is the upper limit of normal for the combined weight of the adrenals of the newborn, it can be stated that the suprarenals in Cases 3 and 5 were hyperplastic. Gross hemorrhages into the adrenals were not recorded in either infant. An increase in the eosinophil elements of the anterior hypophysis was noted in Case 3. It is of interest to find in Case 3 all of the visceral changes—cardiac hypertrophy, extramedullary erythropoiesis, hyperplasia of the islands of Langerhans, adrenal hyperplasia and an increased eosinophilia of the anterior hypophysis.

The following case reports are on the 2 infants who survived, Cases 6 and 7 of Table I.

Case Reports. CASE 1. New Haven Hosp. Unit A, 91722. The mother of this infant was 38 years old and weighed 200 pounds just before this pregnancy. The Kahn test on her blood was negative. Her blood was Rh positive. There were 12 previous pregnancies, 11 of which had resulted in living children and the 12th in a spontaneous abortion. One of the 11 children was a cretin. The present pregnancy was uncomplicated except for headaches

and blurring of vision. Her blood pressures on several occasions were found to be normal, although she had been told that she had a high blood pressure in another hospital when the baby previous to this was born, and although she had been found to have blood pressures of 175/130 and 155/100 in our

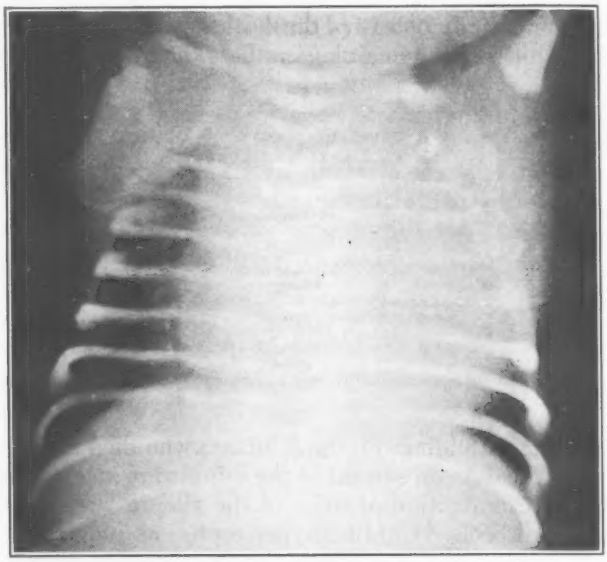

FIG. 1.—Case 1. Age, 1 day. Transverse diameter of heart, 8.1 cm. Transverse diameter of thorax, 11.2 cm. Cardio-thoracic ratio, 72.

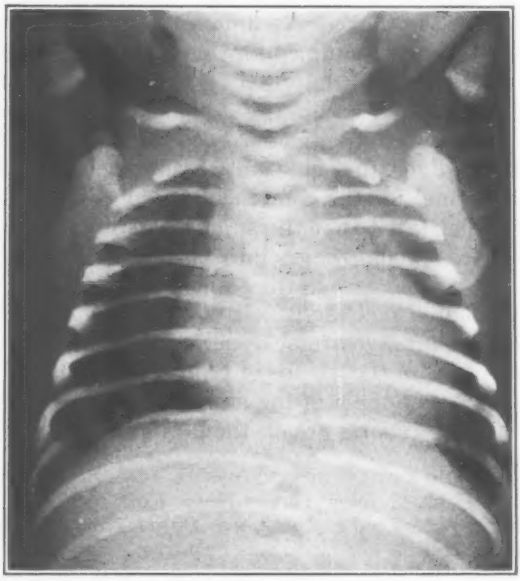

FIG. 2.—Case 1. Age, 5 days. Transverse diameter of heart, 7.1 cm. Transverse diameter of thorax, 10.5 cm. Cardio-thoracic ratio, 68.

Medical Clinic 1 year prior to the present pregnancy. The basis for the hypertension was not established. The urine was negative. Throughout the present pregnancy she was so obese that the fetal parts could not be made out. Labor started spontaneously and the baby was delivered 5 hours later without

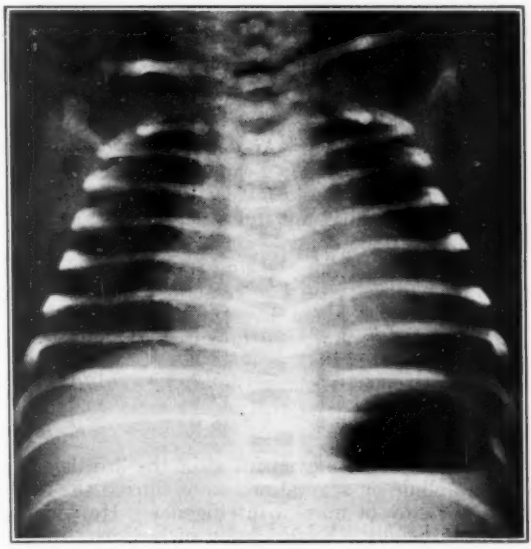

FIG. 3.—Case 1. Age, 7 days. Transverse diameter of heart, 7.1 cm. Transverse diameter of thorax, 10.9 cm. Cardio-thoracic ratio, 65.

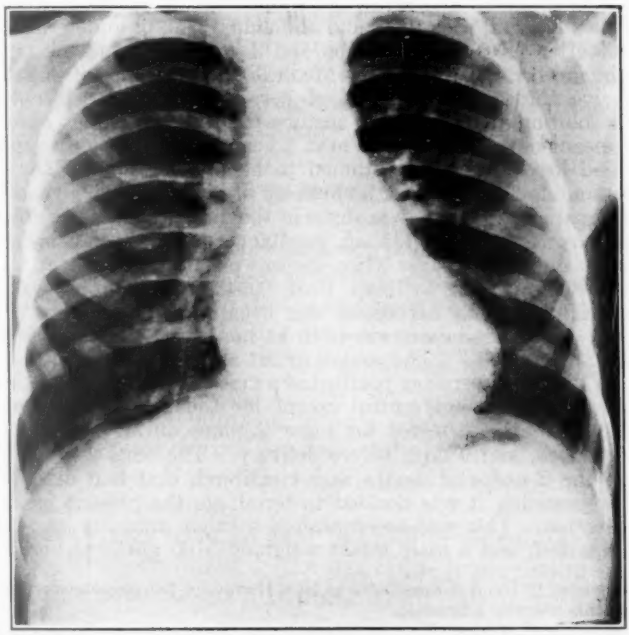

FIG. 4.—Case 1. Age, 5 years. Transverse diameter of heart, 9.4 cm. Transverse diameter of thorax, 19 cm. Cardio-thoracic ratio, 49.

difficulty and without instruments. The baby was a male weighing 4700 gm. The cyanosis which was localized to the head at birth became generalized and marked 2 hours later. He was put in an oxygen tent for the next 48 hours and the cyanosis improved remarkably. Physical examination at birth was not notable except for the presence of a systolic murmur, which disappeared 3 days later, not to be heard again. Roentgen examinations of the heart were made on the 1st day of life and on several occasions thereafter, at a target film distance of 6 feet. The heart remained enlarged during the first 7 days of life as determined by the Roentgen studies (Figs. 1, 2, 3). No further Roentgen ray examinations were made until he was 5 years old, at which time his heart was normal in size and shape (Fig. 4). Cardiac enlargement could not be made out by clinical examination. An ECG done on the 2nd day of life showed the T waves to be diphasic in Lead 1 and the S-T segment to have a peculiar upward convexity in this same lead. Except for S-A tachycardia and right axis deviation, the ECG was not otherwise abnormal. Blood counts were as follows:

Day of life	R.B.C. (millions per c.mm.)	Hg. (gm.%)	W.B.C. (thousands per c.mm.)	Normoblasts (thousands per c.mm.)
1	6.8	18.0	18.3	7.4
2	6.2	18.0	17.1	3.2
4	6.8	18.0	16.0	1.6
5	5.5	18.0	13.0	0.1
6	5.5	17.5		
9	6.2	18.0	12.5	0.0

His course in the hospital was uneventful after the 3rd day of life. He was seen in the follow-up clinic on several occasions during the next 5 years. At 5 he appeared to be a boy of normal intelligence. He weighed 40½ pounds and was 41½ inches in height. Examination of his heart was negative.

Tests for reducing substances in the mother's urine were made routinely in this hospital 2 years and 1 year before the birth of the patient; they were both negative. Similar tests on the mother's urine were found to be negative at the time of his birth and again 18 months later when the mother was admitted to this hospital with fever and abdominal pain of undetermined origin. Six months after the latter admission and 2 years following the birth of the patient, the mother was seen in the Medical Clinic because of pruritus vulvæ and excessive thirst. Examination of her urine showed 4+ reduction of Benedict's solution and a negative acetone test. Her diabetes was regulated solely by means of diet during the next 3 years. Pruritus vulvæ, polydipsia, polyuria and loss of weight continued to be present off and on. She was admitted to another hospital for a check-up of her diabetes 2½ years after the birth of the patient.* There was sugar in the urine and 2 fasting blood sugar determinations were 195 and 145 mg. per 100 cc. at the time of this admission. Her urine became free of sugar when she was put on a diet.

Case 2. Boston Lying-In Hosp. Unit, 9994.† The mother was 36 years old. The Kahn test on her blood was negative. There were 3 previous pregnancies. The first infant was born at home and died on the 15th day of life with "meningitis." The second infant also was born at home and died at birth. The third pregnancy resulted in a macerated fetus. The fourth and present pregnancy was uneventful except for the presence of hydramnios. Her urine was routinely tested for sugar 3 times during this pregnancy: 4 months, 1 month, and 9 days before delivery. The tests were all negative. In view of the 2 neonatal deaths and 1 stillbirth that had occurred in her previous pregnancies, it was decided to terminate the present pregnancy by Cesarean section. This was accomplished without difficulty at term before labor had started, and a male infant weighing 5100 gm. was born. On the

* I am indebted to Dr. A. Capecelatro of New Haven for permission to report the data obtained on this hospital admission.

† Dr. Frederick C. Irving, Visiting Obstetrician, Boston Lying-In Hospital, kindly gave permission for the publication of the data on this infant and mother.

6th day after birth the infant's temperature was 103° and he was noted to be "jittery." The red blood cells were 4.8 million per c.mm. and the hemoglobin was recorded as 90%. No normoblast counts were made. A Roentgen ray of his heart on the 6th day showed that the heart was enlarged, the cardio-thoracic ratio being 60. By the 16th day the cardio-thoracic ratio on the roentgenogram had returned to normal, being 52. The "jitteriness" was present on the 7th day of life but not afterwards. Fever was not present after the 6th day. During the first 5 days of life he lost 13.5% of his birth weight. A systolic murmur was heard over the precordium from the 7th to the 13th day. He was discharged from the hospital at the age of 2 months weighing 6 kg. and in good health. Physical examination at the time of discharge was negative.

Two days after delivery the mother became acutely and suddenly ill. She was found to have fever. An intraäbdominal complication of the operative procedure was considered. An upper respiratory infection and pyelitis were diagnosed. Fasting blood sugar concentrations of 182, 167 and 250 mg. per 100 cc. were found on the 2nd, 3rd and 4th days postpartum. A diagnosis of diabetic acidosis was made and she was treated with insulin. Nine, 15 and 24 days postpartum her fasting blood sugar concentrations were 250, 143 and 182 mg. per 100 cc. Her diabetes improved. The insulin dosage was gradually reduced and she was discharged without any insulin. She was followed in the Out-Patient Clinic of the Beth Israel Hospital in Boston and on her last visit, 9 years after the birth of the patient, 8 to 10 units of protamine zinc insulin daily were again advised in order to better regulate her diabetes.*

Comment. The postmortem findings in the infants in Table 2 are similar to those described in infants born to diabetic mothers.[7,8] The clinical findings in the 2 infants who survived (Cases 1 and 2)—the increased birth weight, cardiac hypertrophy and excessive normoblastemia—are in no way different from those described by Miller and Wilson in some infants born to diabetic mothers. Although the findings are the same in the infants regardless of whether or not maternal hyperglycemia has been established, the absence of diabetic symptoms and signs in the mothers makes the diagnosis of the syndrome in the infants of these mothers more difficult.

The difficulty in diagnosis can be partly overcome by anticipating the presence of the syndrome in infants with an excessive birth weight and newborn infants with cardio-respiratory symptoms. Infants with a birth weight of 4500 gm. or more make up only 1% of the population.[3] Since the syndrome has its highest incidence in this birth-weight group, the routine use of Roentgen studies of the heart and normoblast counts can be expected to aid in establishing the diagnosis in a number of these infants. The exact incidence of the syndrome in this birth-weight group has not been established. The routine employment of Roentgen studies and normoblast counts in infants who have cyanotic spells, dyspnea and tachypnea during the neonatal period regardless of their birth weight will increase the number of infants in whom the diagnosis of this syndrome can be made.

Two important facts must be kept in mind in diagnosing this syndrome in living newborn infants: the size of the heart diminishes very rapidly and the normoblasts disappear from the peripheral blood

* I am indebted to Dr. H. A. Derow, Director, Out-Patient Department, for the information concerning her follow-up visits at the Beth Israel Hospital.

relatively early. Hence, the study of both these conditions should be initiated within the 1st or 2nd day after birth.

The differential diagnosis will include infants with cardiac hypertrophy associated with congenital malformations of the heart or its great vessels. Cardiac hypertrophy associated with malformations would not be expected to return to normal size within the 1st or 2nd month of life as it does in infants born to diabetic mothers or mothers who later develop diabetes.[8] Furthermore, cardiac and respiratory symptoms, when present in the latter group of infants, have not been known to persist beyond the first 10 days of life, while in those with congenital anomalies they frequently persist for weeks and months. Although cardiac murmurs can be heard during the first few days of life in infants with cardiac hypertrophy unassociated with congenital anomalies, they are not known to persist as they so frequently do in infants with congenital heart disease. The possibility that the mother of an infant with a heart that is enlarged as the result of some congenital anomaly might subsequently develop diabetes cannot be excluded. Congenital malformation of the heart among infants born to diabetic mothers has been observed, but it is uncommon.

The differential diagnosis will also include infants with an excessive normoblastemia associated with sepsis, syphilis, premature birth and erythroblastosis fetalis. Serologic tests for syphilis and blood cultures should help to differentiate the first 2 of these. Cardiac hypertrophy has not been described either in newborn infants with syphilis and sepsis or in infants born prematurely. The greatest difficulty will be in differentiating infants with erythroblastosis fetalis from those born to "prediabetic" mothers, since the former not only have a considerable normoblastemia but also cardiac hypertrophy.[7] It has been shown, however, that unless either anemia or jaundice are present the diagnosis of erythroblastosis fetalis must be viewed with considerable doubt.[7] Hence, red blood cell counts in infants with cardiac hypertrophy and normoblastemia will be of the greatest importance in the differential diagnosis. If the infant is stillborn or dies before anemia or jaundice can develop, there is no way yet known of making the differential diagnosis at postmortem between these 2 groups of infants.

The significance of the visceral lesions and their relation to the diabetic syndrome have been discussed in previous papers in detail.[6,7,8] It is sufficient to reiterate here that maternal hyperglycemia can be excluded as a probable cause of the visceral lesions, the oversize of the fetus, and the high fetal and neonatal mortality seen in infants born to diabetic mothers, since all of these changes are in evidence before maternal hyperglycemia can be demonstrated.

Conclusions. 1. A newborn infant can exhibit the same clinical and postmortem changes regardless of whether the mother is diabetic during the gestation period or develops symptoms and signs of diabetes mellitus after the delivery.

2. The changes in the infant can include macrosomia, cardiac hypertrophy, hyperplasia of the islands of Langerhans, excessive extramedul-

lary erythropoiesis, adrenal hyperplasia and an increase in the eosinophil elements of the anterior pituitary gland.

3. The birth of an infant with these findings may be the first sign of impending diabetes mellitus in the mother.

4. The differential diagnosis in newborn infants with the above changes is discussed.

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ACUTE MYOCARDITIS IN INFLUENZA A INFECTIONS

Two Cases of Non-bacterial Myocarditis, With Isolation of Virus From the Lungs

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A patient, who in mid-December, 1942 had a mild illness that might be construed as clinical influenza, became acutely ill early in April, 1943 and died in 6 days. The fatal illness was accompanied by fever, chills, extreme prostration and progressive dyspnea. There was evidence of marked myocardial weakness and diffuse signs appeared in the lung bases before death. Clinically, the findings were interpreted as those of a rapidly progressing primary atypical pneumonia, probably of viral etiology and similar to others which were prevalent at the time. Autopsy revealed a minimum of pathology in the lungs, but the heart showed an extreme degree of acute diffuse myocarditis.

The isolation of a virus from the lungs of this case and its identification as influenza A makes it a very unusual case and prompted this report.

A brief survey of the literature since the discovery of the influenza viruses reveals no instance of acute myocarditis in a human case from which influenza or, indeed, any other virus was isolated and identified. There are, however, a number of clinical and pathologic descriptions of cases with evidence of myocardial damage associated with epidemic influenza. Some of these occurred during the pandemic of 1918 and even earlier, but most of them were observed in smaller outbreaks since that epidemic. They have been recognized chiefly by the symptomatology and by changes in the electrocardiograms. Myocarditis has also been produced experimentally in animals by the injection of a number of different viruses, but the influenza virus is not among them.[41,42] Some of the clinical reports may be summarized briefly.

Circulatory failure was observed with great frequency during and after the pandemic of 1918.[4,13,18,20,23,36] Most writers ascribed this finding and the deaths in such cases to general intoxication from the infection and not to the heart alone. There were many cases in which abnormalities of rate or rhythm and ECG changes suggested cardiac damage especially to the conducting mechanism.[2,3,6,9,14–16,19–23,25–27,–29,33,37,38,40,44,57] Cardiac dilatation has also been observed in infants and children after influenza-like infections.[35] Isolated instances of sudden death during convalescence from influenza associated with dilatation of the right ventricle have been reported.[5,19,46,52] The frequency with which cardiac abnormalities were noted varied considerably. Hyman[21] estimated that cardiac abnormalities complicated influenza in from 5 to 12% of the cases observed in hospitals in London, Berlin, and Boston. Others have felt that they are the most frequent complications of epidemic influenza,[5,12,38] while still others considered them to be quite infrequent,[1,4,32] and many extensive reports on the clinical aspects of influenza make little or no mention of cardiac complications except in relation to the superimposed bacterial infections.

The cardiac disturbances which have been observed—after influenza include bradycardia, extrasystoles, partial and complete heart block, sinus-nodal block, loss of various complexes and T wave changes in the ECG's. Hypotension has been observed frequently, and in many instances the diastolic pressure was found to be low and the pulse pressure increased. The symptoms described as accompanying these findings include weakness, dyspnea, palpitation, anginoid pain, extreme malaise, Stokes-Adams attacks and sudden death. These symptoms are said by some writers to be as common after influenza as they are in mitral stenosis.[5,16] The prognosis, however, is for complete recovery in the postinfluenzal cases in contrast to progression of the symptoms in mitral stenosis. The experience of most clinicians, however, is probably similar to that of MacKenzie,[36] who had never seen a case of influenza in which damage was limited to the heart alone, as in rheumatic fever.

Most of the signs and symptoms mentioned have been ascribed to myocardial weakness or to focal myocarditis. Dilatation of the heart

has also been described. The abnormalities in general are said to be comparable with those seen in various other infections, particularly, scarlet fever and diphtheria, and they are often comparable to the severe myocardial lesions found in the latter. The factor of bacterial infection complicating the influenza in these cases has sometimes,[6,46] but not always, been considered. Such infections may have played an important rôle, as evidenced by the fact that some of the writers have included bacterial endocarditis and purulent pericarditis among the cardiac complications of influenza. The cardiac complications of influenza have been observed infrequently during the acute stage of the disease. More often they have been observed during convalescence. Most writers have noted an almost complete lack of correlation between the severity of the influenza and that of the cardiac findings.

The first case to be presented has the essential characteristics of Fiedler's acute interstitial or acute isolated myocarditis.[10] Most of the reported cases of this condition have been reviewed by Scott and Saphir,[50] Simon and Wolpaw,[51] and Saphir.[47] Two cases resembling the present one and associated with acute respiratory infection have been recently described: one by Hansmann and Schenken[17] and the other by Covey.[7] The first of these is included in Saphir's review, but the latter was reported subsequently and will be discussed later.

A review of the literature on the pathologic changes in the myocardium in influenza reveals considerable differences of opinion. Leichtenstern,[31] writing of the 1889–1890 epidemic, stated that the changes in the heart muscle were due to complicating infections, especially of the lungs, and that such changes were those found in any acute infection, namely, parenchymatous and fatty degeneration. Kuczynski and Wolff,[30] in their review of the 1918 epidemic, found that the myocardium showed no characteristic morphologic changes. Those changes that did occur were only slight and did not exceed those seen in the course of any severe septic illness. Opie[39] stated that the heart muscle showed little evidence of injury, as did Klotz,[28] Winternitz,[55] and Wegelin.[54]

Lucke, Wight, and Kime,[34] reporting on their findings on 126 fatal cases, declared the heart was always more or less affected. However, the myocardial changes they described consisted merely of cloudy swelling and edema of the interstitial tissue.

Saphir,[47] in his comprehensive review of myocarditis, concluded: "Thus, from the reports cited, it seems clear that myocarditis in so-called grip or influenza is exceedingly rare, though myocardial damage which easily may be interpreted as the result of cloudy swelling, may be encountered clinically."

Kirch,[24] reviewing the reports on the 1918 epidemic and recurrences of influenza since then, found that there were degenerative changes in the heart muscle but only very exceptionally an inflammatory process, and this only in the late stages of the disease. He credited Schmorl[49] with being the first to observe this type of myocardial disease.

Schmorl[49] described the pathologic findings in 5 patients who died of

heart failure at varying periods after an attack of influenza. His first case died 10 weeks after a moderately severe attack of influenza uncomplicated by pneumonia. The heart showed an extensive infiltration of round cells and also numerous small scars scattered diffusely throughout the myocardium. Schmorl felt that this lesion represented a late stage of the process found in 3 of his other cases. These 3 showed extensive inflammatory changes affecting the heart muscle accompanied by an interstitial infiltration of plasma cells, round cells and edema. They died suddenly, one 4 weeks and another 5 weeks after the initial illness. The duration of the disease in the 3rd case was not known. The 5th case suffered such severe cardiac damage from an attack of severe influenza and pneumonia that he was unable to return to active duty with the army. The patient died suddenly. At autopsy, his heart was enlarged and microscopically showed numerous acellular scars which, in Schmorl's opinion, were the result of the inflammatory lesions which were similar to those seen in the preceding 3 cases. In summarizing his findings, Schmorl stated that he had never seen such widespread and extensive myocardial damage in any other infectious disease.

Roulet[46] reported 2 patients who died suddenly 2 weeks and 3 weeks respectively following influenza. The myocardium of the 1st case showed extensive acute damage to the muscle fibers associated with an interstitial cellular infiltration. The myocardium of the 2nd case showed much fewer acute lesions, but there were foci where the muscle fibers had disappeared with apparent increase in connective tissue in such areas. Both cases were complicated by streptococcus sepsis, 1 a purulent meningitis, the other a pneumonia with empyema. A streptococcus was cultured from the spleen in both cases and from the meninges in the 1st case. Roulet mentions the similarity of the lesions of the heart in these 2 cases to those seen in streptococcus infections, and states that the rôle of mixed infections is probably much more important in causing damage to the heart than the etiologic agent of influenza. In the introduction to his paper, Roulet mentions the rarity of interstitial infiltrations of the myocardium in the 1918 epidemic. He cited Fahr as having seen it once in 246 autopsies, Glaser and Fritzche once in 350 and Koupmann 7 times in 244 autopsies. The degree of such infiltrations was directly proportional to the severity of the general septic condition of the patients.

Covey,[7] in discussing so-called Fiedler's myocarditis, described a patient who died suddenly 14 days after a "cold." At autopsy, the heart was enlarged and microscopically showed extensive and severe disease of the myocardium, the lesions apparently being of different ages. Covey felt that the type of histologic changes in the lungs and spinal cord favored a viral etiology. He states that in 14 cases of Fiedler's myocarditis where a history of a preceding infection was established, 6 were either influenza or acute upper respiratory infections. He makes no mention in his case report of bacteriologic or virus studies.

Case Reports. CASE 1.* The patient was a 34 year old white woman who, except for recurrent alopecia areata for 10 to 15 years and a mild anemia that was controlled by ferrous sulfate, was in good health until the middle of December, 1942. At that time she had a mild attack of what was called bronchitis or "flu." This attack began a few days after her husband became ill with what was called "virus pneumonia." Serum obtained from the husband after his attack fixed complement with influenza A in a dilution of 1:64, but the patient's serum was not tested. Following this illness, the patient continued to have cough and fatigue. Examinations by her physician during this period revealed no abnormalities of the heart, lungs or blood. She was again seen on February 26, 1943 because the cough and fatigue continued. At that time, the fourth of a series of roentgenograms of the chest revealed no abnormalities and fluoroscopy showed normal heart and lungs.

On the evening of April 4, 1943, the patient noted that she was unusually tired, and on the following morning she had general malaise and some increase in her cough. On April 6, she had chilly sensations, and that evening her temperature rose to 103.4° F. Her lungs at that time were clear. She was put to bed and given aspirin after which she had drenching sweats and a drop in temperature.

On April 9, her condition became much worse. Her temperature was 102.6° F., the pulse was 124 and regular but feeble and thready in character and the blood pressure was 125/78. There was slight dullness and increased whispered voice and tactile fremitus at the right lung base posteriorly. Many moist râles were heard over this area and a few transient râles were heard at the left base. No cardiac enlargement was made out, but the heart sounds, though audible, were faint and distant. The blood counts showed 4 million erythrocytes and 15,000 leukocytes (70% neutrophils). The urine showed 2+ albumin and 2 to 3 W.B.C. The patient raised no sputum, but culture of the throat yielded mostly *Neisseria catarrhalis* and a few colonies of coagulase positive *S. aureus*. The patient was thought to have pneumonia and was given sulfadiazine, 4 gm. initially and then 1 gm. every 4 hours. (She took a total of 8 or 9 gm.)

Late that evening the patient complained of substernal soreness and tightness. She appeared anxious and distressed. The heart sounds were more distant. The pulse was 132 and irregular, due to extrasystole. There was no cardiac enlargement, no cyanosis and no distention of the neck veins. On the morning of April 10, her condition was about the same. The temperature dropped, but the pulse remained rapid and was apparently regular. The signs in the right lung had extended up to the level of the scapula. In the afternoon, she became much worse. Her pulse became weaker and she developed pallor, cold clammy skin, marked anxiety, rapid shallow respiration and a sense of suffocation and substernal constriction.

She was then taken to the Peter Bent Brigham Hospital late in the afternoon. On arrival there, she was extremely ill. Her temperature was 102.2° F, the pulse could not be felt at the wrist and the blood pressure was 80/70 (?). She was restless, anxious, breathing rapidly, and moaning. Her extremities were cold and clammy. The neck veins were not distended. At the right lung base, there was dullness, bronchial breathing and numerous medium moist râles. The breath sounds at the left base were suppressed; and scattered râles were heard throughout the left lung. The heart did not seem enlarged, but the sounds were very faint and distant. The abdomen was distended but non-tender, and the liver and spleen were not felt. The W.B.C. was 20,000, predominantly neutrophils, and these did not show toxic granulations. Sputum could not be obtained.

The patient was given morphin $\frac{1}{6}$ gr. before being sent to the hospital. This was repeated shortly after her arrival when oxygen, administration by mask, was started. She was relatively comfortable after this for about 4 hours, but

* We are indebted to Drs. Lewis Kane and Charles A. Janeway for details of this case, and to Drs. Sidney B. Luria and Orville T. Bailey of the Peter Bent Brigham Hospital, who performed the autopsy.

her condition, otherwise, remained unchanged. A bedside roentgenogram of the chest at that time showed diffuse fine mottling of both lungs with irregular streaky consolidation radiating from the left hilum through most of that lung. There were more localized denser areas near the right cardiac border and at the base of the right upper lobe. There was also a thin layer of fluid discernible along the left axillary border and partly obscuring the costophrenic sulcus. These findings were interpreted as compatible with atypical pneumonia. An ECG showed complete A–V block and extreme slurring of the QRS complexes and was interpreted as indicating an extreme degree of myocardial damage (Fig. 1). The patient failed rapidly and despite the administration of stimulants, she died shortly after midnight.

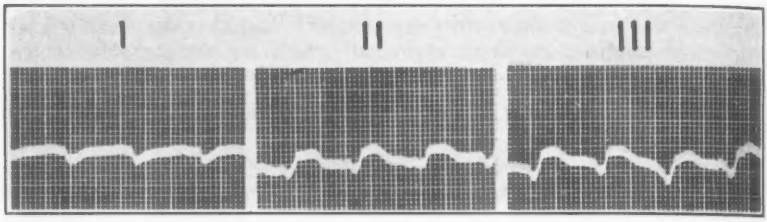

FIG. 1.—Electrocardiogram taken 2 hours before death in Case 1 and showing complete heart block and bizarre ventricular complexes.

AUTOPSY was performed 8 hours after death. Only the pertinent findings are given.

Peritoneal cavity: There were 300 cc. of clear yellow fluid. *Pleural cavities:* Right pleural cavity contained 950 cc. of a pale yellow cloudy fluid with some flecks of fibrin, and the left pleural cavity contained 600 cc. of similar fluid. *Pericardial cavity:* There was 1 small hemorrhagic area 1 x 0.5 cm. overlying the edge of the right ventricle. The pericardial cavity contained approximately 40 cc. of clear yellow fluid.

Heart: Weight 490 gm. Valve measurements were: tricuspid 10 cm., pulmonary 8, mitral 9, aortic 7. The left ventricle was 2 cm. thick, and the right 0.8 cm. The individual chambers of the heart were slightly dilated. The valves were negative. The myocardium was light pink, being somewhat paler than normal. It had the usual consistence and texture. Coronary arteries were negative.

Lungs: Lungs were moderately increased in weight. They were fairly crepitant throughout save posteriorly, especially at the bases where there was less crepitation. On section, a considerable amount of bloody fluid could be expressed from the cut surface. No areas of consolidation were present. The mucosæ of the bronchi were slightly reddened, but were glistening and free from exudate. The blood-vessels were negative.

Microscopic Examination. Heart (Figs. 2 and 3): The myocardium showed very extensive changes. This was true of the walls of all chambers of the heart. The lesions of the cardiac muscle were evidently of different ages. In the earliest stage, the affected muscle fibers were coarsely granular. These coarse granules represented the cross striations which had become much thicker and fewer in number. The longitudinal fibrils were also granular or had completely disappeared. The nuclei of the muscle fibers were usually no longer recognizable. The involved fibers were infiltrated with a few large mononuclears. At a later stage, the muscle fibers became swollen and hyaline with complete loss of both cross striations and longitudinal fibrils. The fibers stained homogeneously and intensely with phloxine and, after staining with Mallory's phosphotungstic acid hematoxylin, they stained red instead of the blue of normal fibers. The necrotic fibers were invaded by varying numbers of

larger mononuclears. In the oldest lesions the necrotic fibers had been completely removed and were replaced by focal collections of larger mononuclears. The necrotizing process involved a small portion of a fiber or it affected the greater part of a fiber. There was an extensive infiltration of the interstitial

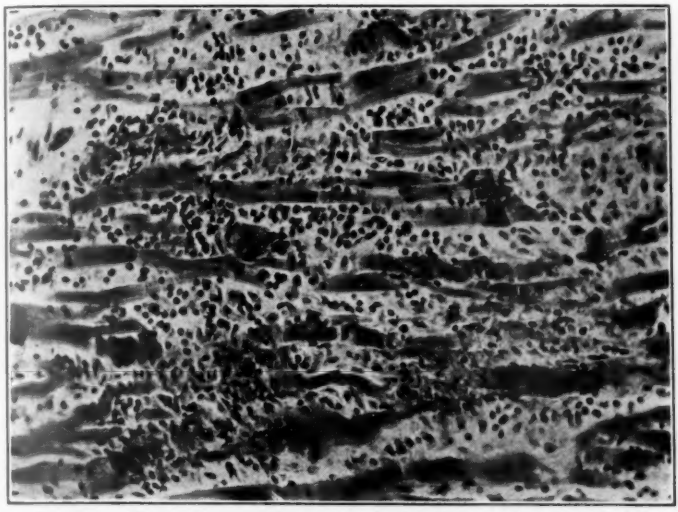

FIG. 2.—Case 1. Myocardium. Necrotic muscle fibers and interstitial infiltration. (Phloxine methylene blue, × 160.)

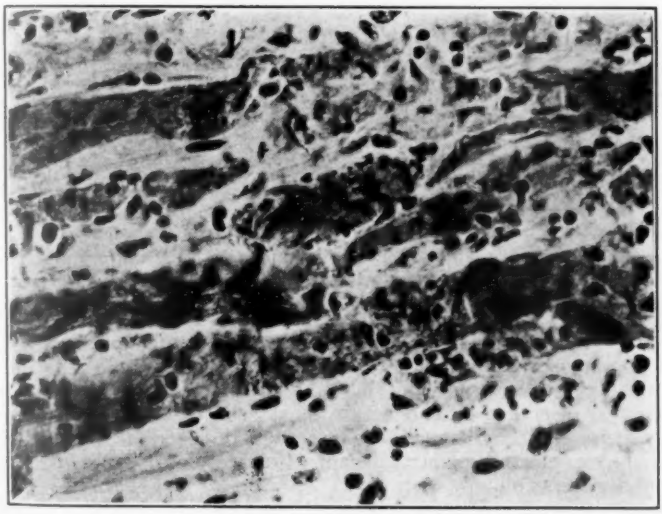

FIG. 3.—Case 1. Myocardium. Necrotic muscle fibers invaded by large mononuclears. (Phloxine methylene blue, × 325.)

tissue with lymphocytes, plasma cells, some large mononuclears and occasional eosinophils and mast cells. This infiltration was most marked in the vicinity of the necrotic muscle fibers. The interstitial connective tissue appeared edematous. The blood-vessels were negative except for an occasional small

vein which showed a subendothelial infiltration of a few large mononuclears, lymphocytes and plasma cells.

The epicardium was edematous and was infiltrated with a few large mononuclears, lymphocytes and plasma cells.

The endocardium was infiltrated with numerous cells similar in type to those seen in the interstitial tissue of the myocardium.

Lungs (Fig. 4): The lungs showed a considerable degree of congestion. The alveoli contained a variable number of large mononuclear cells, many of which had phagocyted carbon. Sections from the right lower lobe showed in addition a perivascular infiltration with a few lymphocytes, plasma cells, eosinophils and an occasional mast cell. In the left upper lobe there was one focus of acute inflammation. Here several alveoli contained polymorphonuclear leukocytes, strands of fibrin and some large mononuclears. The walls of these alveoli were infiltrated with polymorphonuclear leukocytes, plasma cells, lymphocytes and large mononuclears. Stains for bacteria failed to reveal any microörganisms in this lesion. Some of the bronchioles showed a slight infiltration of lymphocytes, plasma cells and a rare polymorphonuclear leukocyte in their walls.

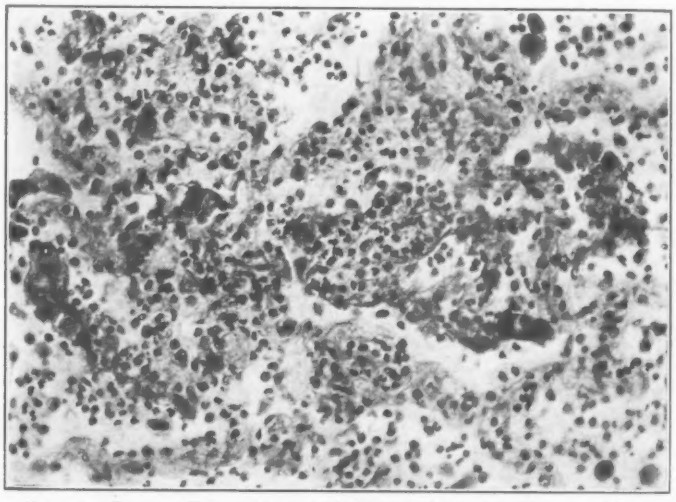

FIG. 4.—Case 1. Lung. Focus of acute inflammation with fibrin and leukocytes in the alveoli. (Phloxine methylene blue, × 160.)

Spleen: The Malpighian corpuscles contained active histiocytes, some of which had phagocyted nuclear débris. There were a few stem cells and myelocytes in the pulp. Several veins showed a subendothelial infiltration of a few lymphocytes, plasma cells and a rare mast cell. *Liver:* There were a few areas of necrosis of the liver cells at the centers of the lobules. A considerable number of liver cells showed fatty degeneration and also, in the central portions, hydropic degeneration.

Kidneys, Adrenals, Bladder, Ovary, Uterus, Aorta, Brain, Pituitary and *Choroid Plexus:* Essentially negative.

Bacteriologic and Chemical Studies. Cultures of the blood, lungs and serous cavities taken at autopsy were negative. No diphtheria bacilli could be cultured from the nose and throat. Serum, pleural and cisternal fluid obtained at autopsy showed no cold agglutinins and no complement fixing antibodies for the psittacosis group (done by Dr. Karl F. Meyer) or for influenza A (PR8 strain). The total protein of the pleural fluid was 1.86 gm.% and its

non-protein nitrogen was 70.6 mg. per 100 cc. The sulfadiazine levels of the plasma was 7 mg. per 100 cc. free and 10.5 mg. per 100 cc. total and of the pleural fluid 7.9 mg. per 100 cc. free and 10.1 mg. per 100 cc. total.

The findings in this case were considered to be sufficiently rare and important to warrant a further search for evidence of similar cardiac lesions in other cases of influenza. For this purpose, there was available material from the 8 cases of staphylococcal pneumonia which occurred as complications of influenza in the epidemic of 1940–41 and were described by Wollenman and Finland.[56] The evidence suggested that these cases probably began as influenza A infections.[43] Cardiac symptoms had occurred in the so-called chronic cases of this group, and were considered to be secondary to pulmonary fibrosis.[11] In 1 case of this series abscesses were found in the myocardium as part of a staphylococcal septicemia but no other cardiac lesions were found. Autopsies in one other sporadic case and in 4 cases which occurred during the epidemic of 1943–44 were also available. Influenza A was isolated from all but 1 of these 5 cases. Lesions were found in the heart of one of the epidemic cases. A brief report of this case follows.

Case 2. An extremely ill 39 year old Italian iron worker was admitted to the Boston City Hospital January 31, 1944 complaining of breathlessness and hemoptysis of 2 days duration. He was apparently in good health until January 23 when he had a slight "head cold" which was followed by general malaise, apathy, anorexia, and prostration. On January 26, he had several shaking chills followed by feverishness. On January 29, he began to have marked dyspnea and cyanosis accompanying a severe cough which was productive of grossly bloody sputum and which continued to the time of entry. He also had 2 attacks of substernal pain and some vague pains in his legs. The patient denied all previous symptoms of cardiorespiratory illness.

On admission, the patient was markedly cyanotic and dyspneic with audible tracheal râles. He was coughing and raising sputum containing dark red blood. His temperature was 98.4° F., pulse 100 and regular, respirations 28 and blood pressure 138/88. Respirations were labored with a prolonged expiratory phase. Throughout both lungs there was diminished resonance without definite signs of consolidation, but with numerous medium and coarse moist râles, most marked in expiration. The heart was not enlarged to percussion but the heart sounds could not be heard because of the loud respiratory sounds.

The W.B.C. was 19,000 (88% neutrophils); the hemoglobin 96%. Sputum showed gram-positive cocci and bacilli, but no acid-fast organisms. The blood non-protein nitrogen was 134 mg. per 100 cc. An electrocardiogram showed sino-auricular tachycardia, left axis deviation, upright T waves and a PR interval of 0.18. A bedside roentgenogram of the chest showed faint diffuse clouding of both lung fields with small irregular, scattered, fluffy and nodular densities.

Oxygen therapy and the usual supportive measures failed to bring about improvement and the patient died early on the morning of February 1, about 14 hours after entry.

Autopsy (14 hours after death). Only a brief description of the gross and microscopic findings in the heart and lungs is given since this case will be reported in detail elsewhere.

The *heart* weighed 330 gm. The auricles and ventricles were not dilated or hypertrophied. The coronary arteries showed atheromatous thickening but no actual occlusions. The interventricular septum contained a fibrous scar about 2 cm. in diameter. The valves were negative.

Lungs. The right weighed 1250 gm. and the left 1110 gm. Both were subcrepitant throughout. On section, no definite areas of consolidation were seen but all lobes felt much firmer than normal. The trachea and bronchi contained a slightly mucoid, serosanguineous exudate.

Microscopic Examination. The *myocardium* showed large areas of scarring composed of dense collagen. There was necrosis of single muscle fibers which were invaded by large mononuclears. The interstitial tissue was infiltrated in areas with large mononuclears, lymphocytes, plasma cells, eosinophils and polymorphonuclear leukocytes (Fig. 5).

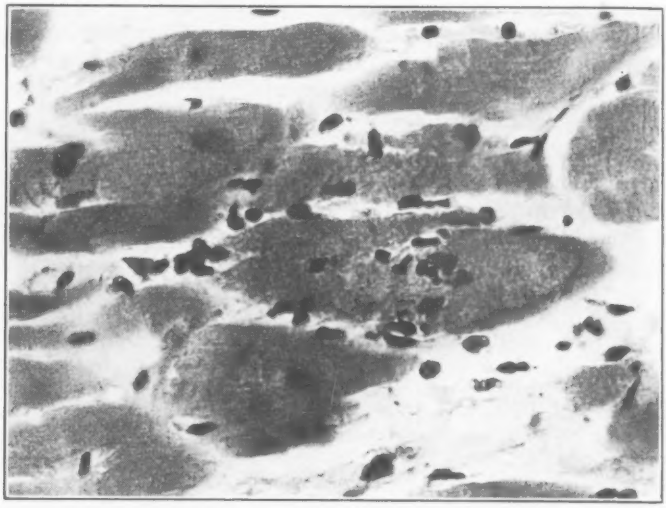

FIG. 5.—Case 2. Myocardium. Two necrotic muscle fibers invaded by large mononuclears. (Phloxine methylene blue, × 750.)

The *lungs* throughout showed the same histologic picture. Some alveoli contained macrophages, the majority of which were filled with carbon. Other alveoli contained a small amount of albuminous precipitate, a few red blood cells and delicate strands of fibrin. Still others showed adherent to their walls a hyaline membrane in which there were often embedded a few polymorphonuclear leukocytes. The alveolar capillaries contained rather numerous polymorphonuclear leukocytes. There were also acute focal lesions in the capillaries, consisting of fibrin and neutrophils.

Virus Isolation and Identification. Some of the hemorrhagic portions of the lung of Case 1 were removed with sterile precautions and stored at −70° C. in a carbon dioxide freezing box. A 20% suspension of ground-up lung was filtered through a Berkefeld "V" filter and the sterile filtrate was used for intranasal inoculation in anesthetized mice and for inoculation into the allantoic sac of 11 to 12 day old chick embryos. The first attempts were unsuccessful and were abandoned in each instance after 6 passages. A second attempt was then made beginning with a different part of the lung treated in the same manner. The mice of the first passage showed no specific lesions and 2 of 4 mice of the second passage showed minimal lesions. In the third passage 4 or 6 mice became ill on the 3rd day and died with extensive lesions on the 4th and 5th days. These 4 mice were used for further serial passage. The other 2 remained well until the 7th day and were then shown to be immune to influenza A. They were each given a challenge dose of about 100 lethal doses of PR8 virus and survived.

Virulence tests were done with the viruses of the 5th and 14th passage. The

50% lethal end-point was between 10^{-5} and 10^{-6} ml. with the former and between 10^{-6} and 10^{-7} ml. with the latter. The 38th mouse passage was again proven to be influenza A by neutralization test. A 10^{-5} dilution of this virus was used. One group of mice received the virus together with serial dilutions of influenza A (PR8) ferret antiserum. All these mice survived and showed no lesions when sacrificed. The same test was done with influenza B (Lee) ferret antiserum.* All these mice and control mice which received virus without antiserum died with typical lesions.

In the egg inoculations from this suspension of the patient's lung, the virus was well established by the 6th passage as shown by the marked and immediate agglutination of the chick cells in the allantoic fluid. Virus from the allantoic fluid agglutinated hen's red cells up to a dilution of 1:2048. The agglutination of a 1:128 dilution of the virus was inhibited by anti-influenzal A (PR8) rabbit serum out to 1:1024 and by anti-influenza B (Lee) rabbit serum only in a 1:32 dilution. All of these findings establish the identity of this virus as a strain of influenza A closely related to PR8.

In Case 2, a sterile filtrate prepared from an area of hemorrhagic consolidation was inoculated into mice and eggs in the same manner as in Case 1. The first attempt in mice yielded lesions only on the 6th passage and deaths with typical lesions on the 7th passage. The 12th passage of mouse virus was fatal in 10^{-6} dilution. Neutralization tests with the mouse virus and immune ferret serum showed definite protection of mice by anti-PR8 serum but not by anti-Lee B serum.

The same material injected into the allantoic cavity of eggs yielded a growth of virus in the first egg as evidenced by the agglutination of the chick cells on removal of the allantoic fluid. Egg passages were continued and virus from allantoic fluid of the 9th passage was used for identification. This virus agglutinated hen cells out to a dilution of 1:512. The agglutination of a 1:32 dilution of this virus was inhibited by anti-influenza A rabbit serum (PR8) to a dilution of 1:128 and it was not inhibited by anti-Lee influenza Type B rabbit serum in a 1:16 dilution (the lowest dilution used).

Serum obtained from the patient's heart's blood postmortem inhibited the agglutination of hen cells with PR8 virus in a dilution of 1:8 but not in 1:16.

Discussion. The course of events in Case 1 and particularly the possible relation of the influenza A virus to the various episodes and symptoms are difficult to interpret with the data available. The history of an influenza-like illness in December coupled with the respiratory infection in the husband who was found to have a significant titer of antibodies against influenza A after that attack, suggest the possibility that the patient's illness was also an infection with the same virus. If that were true, it might account for the persistent cough and fatigue which followed that attack, but there were no discernible anatomic changes to account for these symptoms. The lesions in the lungs were certainly of recent origin and those in the heart only somewhat older since there is no evidence of repair and fibrosis.

From a clinical point of view, two possibilities suggest themselves, both of which are based partly on speculation. The patient may have had an infection with influenza A in December and continued to harbor the virus with mild relapses from time to time until the final and fatal attack when the influenza A was isolated. In that event, the cardiac lesion, if indeed it was an influenzal viral infection, may be regarded as part of the effects of the final invasion of the virus. The

* The anti-PR8 and anti-Lee ferret and rabbit serums were obtained from Dr. F. L. Horsfall, Jr.

alternative possibility is that the patient had a new infection from without, either at the end of February or sometime early in April, which accounted for the final illness and caused the myocardial lesion.

It is interesting, as mentioned earlier, that most of the reported clinical cases of cardiac lesions complicating influenza have occurred during convalescence and sometimes long after apparent recovery from the influenzal infections. Only rarely have such lesions, whether demonstrated at autopsy or by ECG, occurred as part of a severe and rapidly fatal acute attack of influenza. The few cases of isolated myocarditis associated with acute respiratory infections have similar time relations. The virus nature of the previously reported cases, however, is only a conjecture since viruses were not isolated. In this case, influenza A was isolated and identified. Its relation to the cardiac lesion, though only circumstantial, seems very probable.

The course and findings in Case 2 are those of an acutely fatal pneumonia complicating influenza A. The virus was obtained from the lungs which showed characteristic lesions of the virus infection. No significant bacterial pathogens could be cultured from these lungs and they did not show evidence of bacterial infection. The total duration of illness from the first symptom of a "cold" until death, was about 9 days. The pneumonia may have begun either at the time of the chills 6 days before he died or with the onset of dyspnea and cyanosis 3 days later. In the latter event, the chills may have marked the onset of the influenza. The lesions in the heart in this case were slight and limited in extent and were discovered only after careful search. Nevertheless, they were similar in character to those seen in Case 1.

The autopsy on Case 1 revealed an extensive acute myocarditis with necrosis of numerous muscle fibers, accompanied by an interstitial infiltration of various types of cells. As in some other cases reported in the past, the lesions varied from early acute necrosis to complete disappearance of the muscle fibers. There was no scar formation nor regeneration of muscle fibers. It may be of interest, perhaps, to attempt to estimate the age of the myocarditis. The histologic findings are similar to those in Schmorl's second case in which death occurred 4 weeks after an attack of influenza and also correspond to those of Roulet's first case in which death occurred 2 weeks after influenza. Covey's patient, the duration of whose illness was 13 days, had lesions in his myocardium essentially similar to those of our case. It would, therefore, seem justifiable to assume that the myocarditis in our patient was of approximately 2 to 4 weeks' duration. Such a period of time would correspond to the experience of others who state that myocarditis in influenza develops only in the late stages of the disease. That the heart was enlarged was not surprising in view of the extent of the inflammatory process, and such increases in size have been noted by other observers.

The histologic findings in the lungs deserve comment in view of the clinical picture and the fact that an influenza virus was isolated from them. As indicated in the description of the autopsy, the lungs showed surprisingly few pathologic changes. The only evidence of an acute

process was a small focus involving a few alveoli in the left upper lobe. There was no edema or hemorrhage so characteristic of influenzal pneumonitis. The fact that cultures for bacteria yielded no growth and stains for bacteria in the one inflammatory lesion seen were negative, would favor the viral etiology of this lesion.

Myocardial lesions have been described as occurring occasionally in certain virus and rickettsial diseases such as typhus fever, Rocky Mountain spotted fever, psittacosis, yellow fever, measles, mumps, variola and varicella. Myocarditis in foot and mouth disease in cattle and swine has been reported as a not unusual finding.[48] Furthermore, Pearce[41] has produced myocardial lesions experimentally in animals, utilizing for this purpose vaccinia, pseudorabies, inflammatory fibroma, strain A, and myxoma.

From the studies of some viruses, it is apparent that the myocardial lesions are due to the actual presence of the virus. However, it would seem possible that this is not necessarily true of all viruses, especially in view of the work of Rake and Jones,[45] who demonstrated that toxic products could be obtained from cultures of lymphogranuloma venereum.

In our case, no attempt was made to isolate a virus from the heart muscle. Since the virus of influenza is not characterized by the formation of inclusion bodies or other visible evidence of its presence, histologic examination of the lesions is of no assistance in determining whether they are due to the actual presence of the virus or its theoretically possible toxic products. The type of myocarditis resembles most closely that due to diphtheria toxin, which fact might possibly favor a toxic rather than an infectious origin of the lesions.

In Case 2, the duration of the disease was 6 to 9 days. The lesions in the heart muscle consisted of necrosis of occasional muscle fibers. In addition, there was a moderate cellular infiltration of the interstitial tissue. This patient died from his pulmonary infection, whereas Case 1 died of cardiac failure. It has been pointed out by Schmorl[49] that in cases of influenza dying of causes other than heart failure, it may require prolonged and diligent search for evidence of myocardial damage. This statement would seem to hold true here. The lesions, while comparatively few in number, differ from those of Case 1 only in their rarity, not their type. In Case 2, as in Case 1, cultures yielded no bacteria, but a virus was isolated from the lungs. Histologically, there was no evidence of bacterial infection of the lungs, but the picture was that of an acute influenzal pneumonitis.

Summary and Conclusions. 1. Two cases with pathologic findings of acute non-bacterial myocarditis are reported. One of these patients died of cardiac failure and had a minimum of involvement of the lungs; the other died of an extensive acute bronchopneumonia from which no significant bacterial pathogen could be recovered. Influenza A virus was isolated from the lungs of both cases.

2. A review of the literature concerning the clinical and pathologic aspects of acute myocarditis complicating influenza and similar respiratory infections is presented. The relation of the influenza virus to the cardiac lesions in the present cases is discussed.

3. It is suggested that the myocardial lesions in these cases are the result of infection with influenza A virus.

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PROVOCATIVE PROLONGATION OF THE P–R INTERVAL IN RHEUMATIC FEVER*

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The clinical recognition of cardiac involvement in acute rheumatic fever frequently is very difficult. Numerous studies have established the value of the electrocardiogram as the most sensitive and dependable indicator of cardiac involvement in rheumatic fever. Murmurs, enlargement of the heart, gallop rhythm, pericardial effusion and other clinical findings occur in only a small minority of cases in the initial stages of carditis and so are of rather limited diagnostic value.

The most frequent and most specific electrocardiographic sign of carditis is impairment of atrio-ventricular conduction, *i. e.*, prolongation of the P–R interval. The frequency of prolongation of the P–R interval varies greatly in published reports. It is generally recognized that this sign is inconstant and frequently transitory. Even where serial or even daily tracings are employed, a procedure hardly practical as a routine, prolongation of the P–R interval is detected in only about one-half of cases, averaging the reports of various investigators.[9]

It is our purpose to report a simple procedure which appears to enhance the diagnostic value of prolongation of the P–R interval in acute rheumatic fever.

A study of the effect of carotid sinus pressure on the P–R interval was carried out in 16 cases with rheumatic fever, and in 16 control subjects who were hospitalized for miscellaneous infectious diseases, such as scarlet fever, pneumonia, and upper respiratory infections. Electrocardiograms were recorded during right, left, and bilateral carotid sinus pressure both in sitting and recumbent positions. In most cases similar studies were also carried out 20 minutes following intramuscular administration of 1 cc. of 1:2000 prostigmin.

In none of the control subjects did any prolongation of the P–R interval exceeding 0.01 second more than the control occur on carotid sinus stimulation with or without prostigmin. On the other hand, definite prolongation of the P–R interval was observed in 12 of the 16 cases with rheumatic fever. In 2 of the 4 cases with rheumatic fever in whom no prolongation of conduction occurred prostigmin was not given; and as will be shown prostigmin augments the effect in many cases.

* Presented at the New York Heart Association, May 2, 1944.

Case Illustrations. CASE 1 (Fig. 1). H. G., a boy of 13, developed acute rheumatic fever in May 1942. Signs of activity persisted for 3 months with residual mitral insufficiency, as indicated by an apical systolic murmur and slight backward displacement of the esophagus revealing early left atrial enlargement. The P–R interval which varied between 0.20 to 0.28 second remained prolonged for a period exceeding 18 months after all other signs of

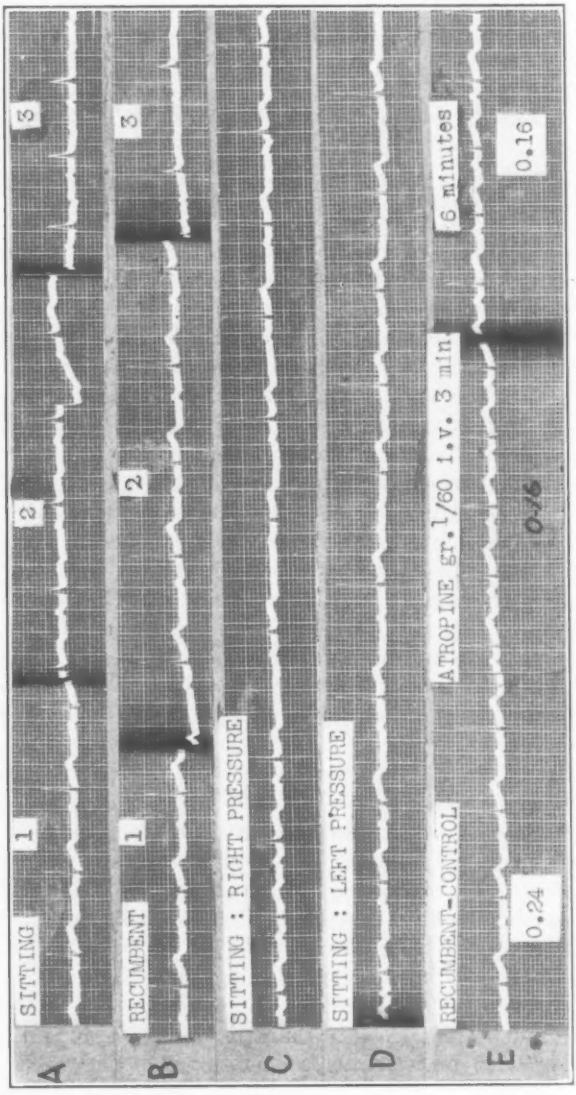

FIG. 1.—Case 1. P–R interval prolongs to 0.28 second in recumbent position (*B*), normal (0.18 second) in sitting position (*A*). Pressure on left carotid sinus (*D*) in sitting position prolongs P–R from 0.18 to 0.30 second, whereas right carotid pressure (*C*) is without effect on conduction time. Atropine (*E*) given intravenously promptly shortens P–R to 0.16 second.

rheumatic activity had subsided. The persistent prolongation of the P–R interval was evident only in the recumbent position, conduction being within normal limits when sitting. Pressure on the left carotid sinus, but not on the right, increased the P–R interval from 0.18 to 0.30 second in the sitting position. The prolonged conduction was abolished promptly by intravenous administration of 1 mg. of atropine.

While in Case 1 the changes in atrio-ventricular conduction occurred when other evidences of active carditis no longer were present, more frequently, as illustrated in Figure 2, the effect of carotid pressure in prolonging the P–R interval is maximal in the initial acute stages of carditis and can no longer be elicited after signs of rheumatic activity have subsided.

Case 2 (Fig. 2). R. V., a male, age 20, gave a history of a previous attack of rheumatic fever 5 years before. He was hospitalized on Feb. 29, 1944, because of fever and polyarthritis involving the right knee and both ankle joints. These symptoms began 3 days before admission and 2 weeks following a cold and sore throat. On examination a systolic apical murmur was heard, pulse rate was 104, leukocyte count 12,300, sedimentation rate 108 mm. in 1 hour, and blood ascorbic acid level reduced to 0.3 mg. per 100 cc. The electrocardiogram (Fig. 2) showed a slight prolongation of the P–R interval to 0.21 second with increase in conduction to 0.24 second on right carotid pressure in the sitting position. A second electrocardiogram 4 weeks after admission, at which time clinical evidence of rheumatic activity had subsided showed a P–R interval of 0.17 second, with no change in carotid pressure. Further electrocardiographic study on April 8, 1944, similarly showed normal atrio-ventricular conduction with no prolongation on carotid pressure or on pressure after intramuscular administration of 1 cc. of 1:2000 prostigmin.

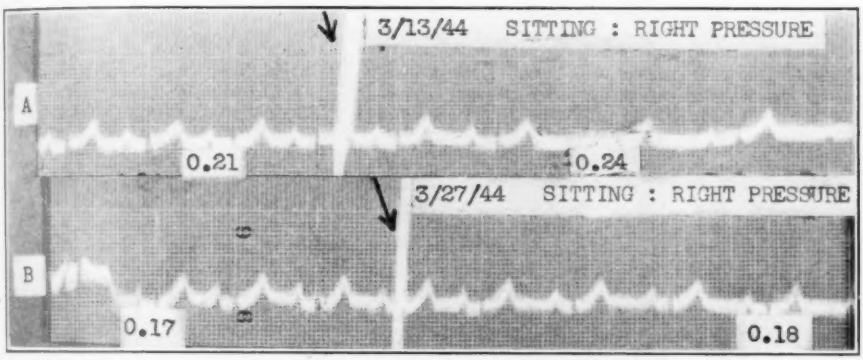

Fig. 2.—Case 2. *A*, Application of carotid pressure (arrow) abruptly lengthens P–R from 0.21 to 0.24 second. *B*, Repetition of carotid pressure test after subsidence of signs of acute carditis shows no effect on conduction time.

Usually, as illustrated in Figure 3, the effect of carotid pressure is greater on the left than on the right, and in the sitting more than in the recumbent position.

Case 3 (Fig. 3). R. M., male, age 26, 3 weeks after scarlet fever, developed polyarthritis and an accelerated sedimentation rate. An electrocardiogram a few days after admission to the hospital was normal, the P–R interval measuring 0.20 second. In the sitting position pressure on the right carotid sinus prolonged conduction to 0.24 second. Pressure on the left caused even greater prolongation to 0.36 second. One month after discharge from the hospital the carotid pressure test was repeated. The P–R interval was unaffected and did not become prolonged on carotid pressure following administration of prostigmin.

Occasionally prolongation of the P–R interval occurs only on right and not on left carotid pressure, although more often the reverse is true.

CASE 4 (Fig. 4). R. R., a male of 18, was hospitalized on March 7, 1944, with an onset of polyarthritis 3 days before admission. Leukocyte count was 12,000, sedimentation rate 80 mm. settling in 1 hour, blood ascorbic acid level 0.5 mg. per 100 cc. An apical systolic murmur was present. The P–R interval measured 0.20 second. Pressure on the left carotid sinus did not affect the conduction time but pressure on the right carotid sinus prolonged the P–R interval from 0.20 to 0.28 second, with transient slowing of the heart rate.

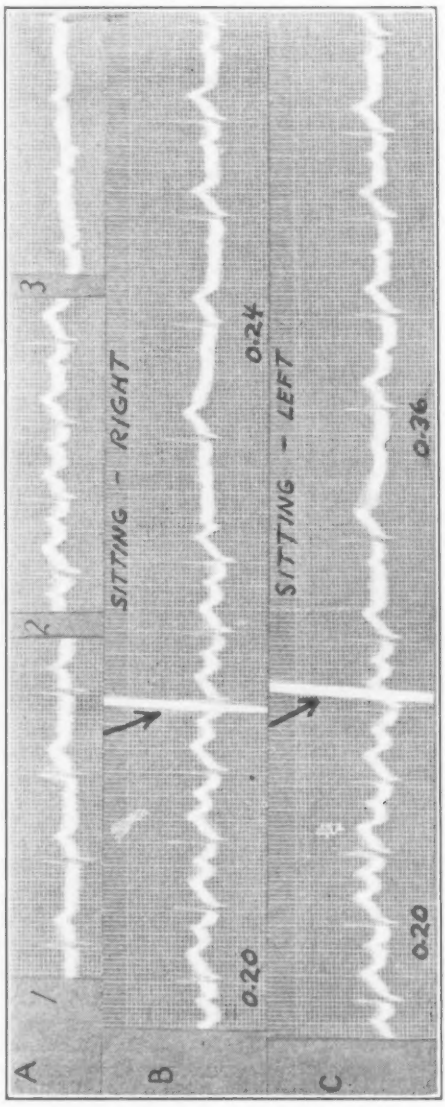

FIG. 3. Case 3. Pressure on left carotid sinus (*C*) prolongs P–R interval from 0.20 to 0.36 second. Right carotid pressure (*B*) causes less marked prolongation to 0.24 second.

CASE 5 (Fig. 5). V. B., male of 18 years, was hospitalized on Feb. 10, 1944, because of polyarthritis developing after a sore throat. Leukocyte count was

elevated to 14,800, sedimentation rate was 80 mm., settling in 1 hour. Apart from tachycardia there were no abnormal cardiac findings. The ECG was negative except for slight right axis deviation which could be attributed to

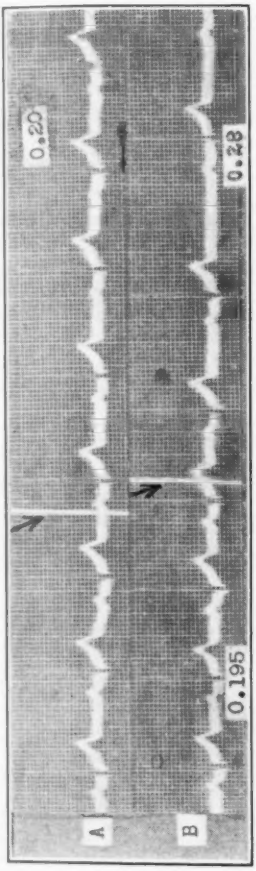

FIG. 4.—Case 4. Left carotid pressure (*A*) has no effect on conduction time, whereas right carotid pressure (*B*) prolongs the P–R to 0.28 second.

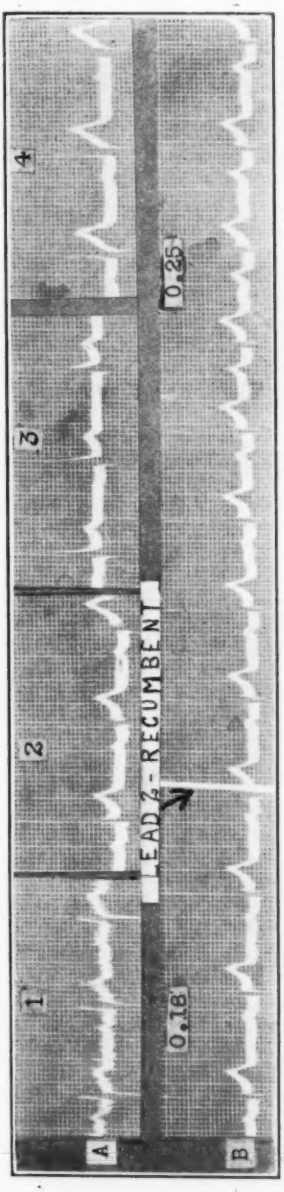

FIG. 5.—Case 5. *A*, Normal electrocardiogram in case of acute rheumatic fever. Right axis deviation is present. *B*, Pressure on the right carotid sinus in the recumbent position prolongs the P–R interval from 0.18 to 0.25 second. The amplitude and width of the P waves are increased during pressure.

slender body build. Pressure on the right carotid sinus in the recumbent position prolonged the P–R interval from 0.18 to 0.25 second. Two months later, at which time all signs of rheumatic activity had subsided, the test was

repeated and no prolongation of the P–R interval could be induced by pressure, or pressure plus prostigmin.

Where carotid sinus pressure alone is ineffective preliminary intramuscular administration of 1 cc. of 1:2000 prostigmin 20 minutes

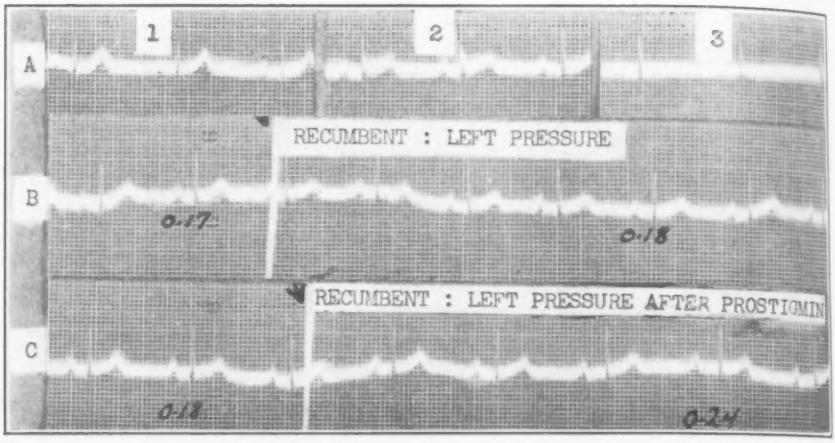

FIG. 6.—Case 6. *A*, Normal electrocardiogram in subject with acute rheumatic fever. Pressure on the left carotid sinus (*B*) is without effect on conduction, but following prostigmin (*C*) left carotid pressure prolongs the P–R interval from 0.18 to 0.24 second.

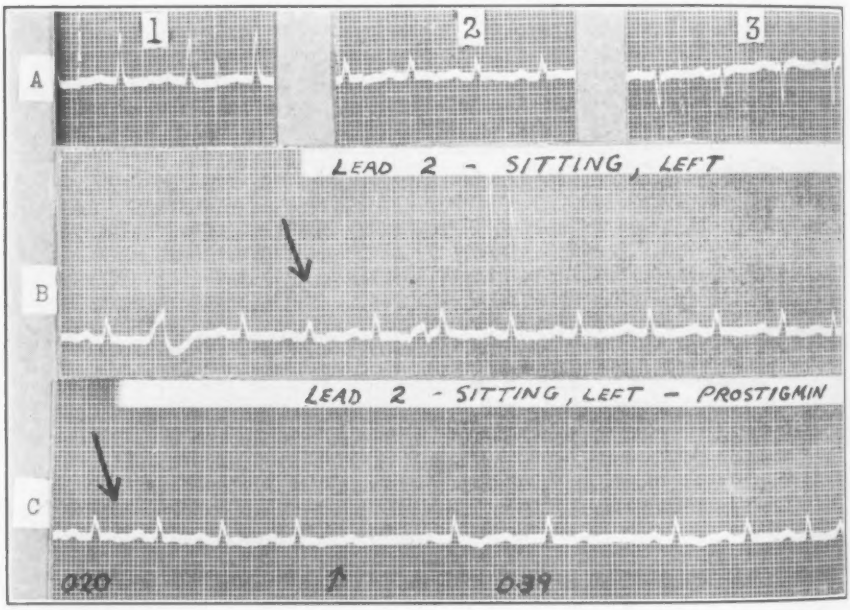

FIG. 7.—Case 7. *A*, Pressure alone in this subject with acute rheumatic carditis and pericarditis is without effect on conduction (*B*). Following prostigmin (*C*) left carotid pressure prolongs the P–R from 0.20 to 0.39 second with dropped beats.

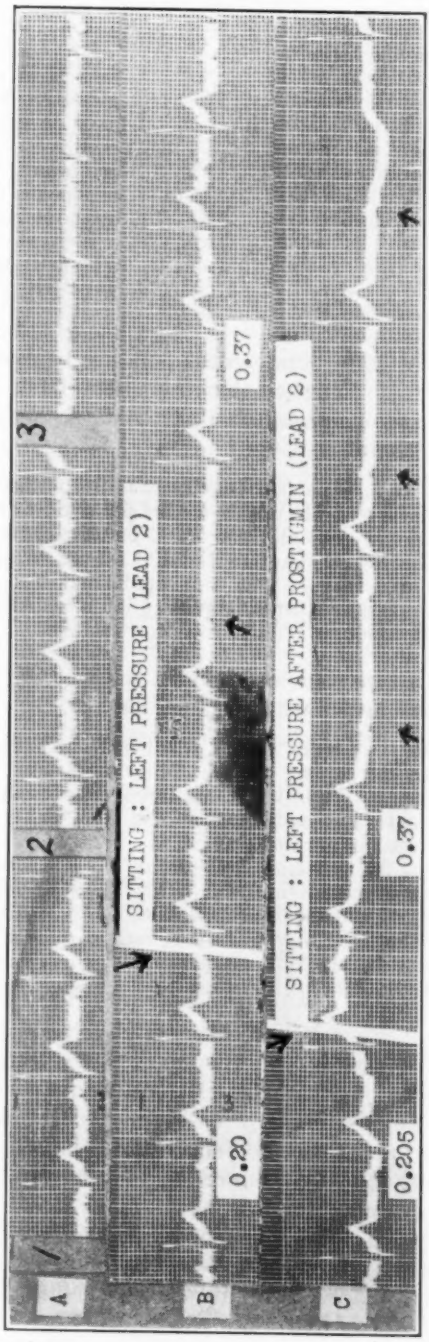

FIG. 8.—Case 8. *A*, Control electrocardiogram is normal. *B*, Following left pressure P–R lengthens from 0.20 to 0.37 second, with dropped beat. *C*, After prostigmin left carotid pressure causes 2 to 1 partial heart block with marked prolongation of the P–R in the conducted beats.

before the test may serve to induce prolongation of the P–R interval on carotid pressure. In none of the cases studied did prostigmin alone prolong atrio-ventricular conduction.

CASE 6 (Fig. 6). E. D., a male, age 27, was hospitalized March 14, 1944, because of polyarthritis of 5 days duration. Leukocyte count was 12,000 and blood ascorbic acid was reduced to 0.4 mg. per 100 cc. There were no abnormal cardiac findings and the ECG (Fig. 5) was normal. Pressure alone did not appreciably alter the P–R interval but when repeated 20 minutes following the intramuscular administration of prostigmin the P–R interval became prolonged from 0.18 to 0.24 second. Five weeks later, at which time the patient had been discharged and all signs of rheumatic activity had subsided, prostigmin and carotid pressure had no effect on the P–R interval, such as occurred during the acute stage of rheumatic fever.

The effect of prostigmin plus carotid pressure is shown even more strikingly in Figure 7. Pressure alone had little effect but following prostigmin marked prolongation from 0.20 to 0.39 second, with dropped beats, occurred on carotid pressure.

CASE 7 (Fig. 7). R. S., a female, age 29, was hospitalized because of a nodular erythema of the lower extremities, arthralgias and fever. Tachycardia and gallop rhythm were present and precordial pain and a friction rub indicated pericarditis. T-wave changes in the ECG were present. The P–R interval, which measured 0.20 second, was unaffected by carotid pressure alone, but following prostigmin carotid pressure induced partial heart block, with the P–R interval prolonged to 0.39 second.

Even more striking partial heart block induced by pressure, and pressure plus prostigmin is illustrated in Figure 8.

CASE 8 (Fig. 8). R. B., a male, age 18, was hospitalized Feb. 21, 1944, for migrating polyarthritis developing 2 weeks following a sore throat. Fever, tachycardia, leukocytosis (W.B.C. 13,000), accelerated sedimentation rate (70 mm. in 1 hour) and low blood ascorbic acid (0.3 mg. per 100 cc.) were present. An apical systolic murmur was heard. The ECG was normal, the P–R interval measuring 0.20 second. Pressure on the left carotid sinus in the sitting position prolonged conduction to 0.37 second, with one dropped beat. Following prostigmin left carotid pressure induced 2 to 1 partial heart block with prolongation of the P–R interval to 0.37 second. A subsequent test of this subject, carried out at the time of discharge for convalescent care, was entirely negative, with no effect from pressure, or pressure plus prostigmin.

Comment. Bruenn,[1] Keith,[6] and others[13] have shown that the prolongation of the P–R interval in rheumatic fever frequently can be abolished by atropine. This suggests that the impairment of atrio-ventricular conduction is in many cases due to a heightened vagal effect rather than to an intrinsic defect in the conduction mechanism. Our own experiments showing the increased sensitivity to vagal stimulation are further evidence for this view. This does not necessarily signify a greater vagal tone as such. The action of the vagus is determined, not only by the release of acetyl choline, but also by the rate of destruction of acetyl choline by the tissue enzyme choline esterase, as first shown by Loewi and Navratil.[7]

The activity of choline esterase is greatly modified by the pH, its action being maximal in an alkaline medium and falling sharply as

the pH shifts toward the acid side as Glick[3] has demonstrated. If the maximum choline esterase activity at pH 8.4 be considered as 1, the activity at pH 8 is 96%; at pH 7, 49%; at pH 6, 16%. Inflammatory tissue as Schade,[11] Valy Menkin,[8] and others have shown is characterized by a lowering of pH, due to accumulation of acid metabolites. Heymans and his co-workers,[5] Richard,[10] and recently Smith and Wilson[12] have shown further that the heart is rendered much more sensitive to the action of acetyl choline by anoxemia, which presumably likewise acts by decreasing the pH in the myocardium inhibiting the effect of choline esterase.

Gross and Fried,[4] in a study of lesions in the atrio-ventricular conduction system occurring in rheumatic fever, have shown that in two-thirds and probably more of cases with rheumatic fever coming to autopsy, "a variety of inflammatory and vascular phenomena within the horizontal conduction system as well as in the surrounding tissues" occur. We suggest that the inflammatory process and vascular changes in the region of the conduction system, by lowering the pH and interfering with tissue nutrition inhibit choline esterase, allowing potentiated vagal effect, which is responsible for prolongation of atrio-ventricular conduction.

Summary. 1. Carotid stimulation prolongs the P–R interval very frequently in acute rheumatic fever.

2. The effect is more marked when the P–R interval is initially 0.18 to 0.20 second than when it is less than 0.18 second, vagal stimulation intensifying latent impairment in atrio-ventricular conduction.

3. The effect of carotid pressure on conduction is maximal during the acute stage of carditis, and frequently disappears as rheumatic activity subsides.

4. Prolongation occurs more commonly in the sitting than in the recumbent position, and more often with left than with right carotid pressure.

5. In many cases the effect is augmented by preliminary administration of prostigmin. Prostigmin alone, in the dose employed, does not prolong the P–R interval. Dameshek, Loman and Myerson[2] likewise observed that prostigmin has no effect on the P–R interval. Mecholyl, however, as reported by these investigators, may considerably prolong atrio-ventricular conduction in normal subjects.

Conclusions. 1. Impairment of atrio-ventricular conduction of considerable degree was induced in 12 of 16 subjects with rheumatic carditis by pressure on the carotid sinus. Similar pressure has produced no such impairment in 16 control cases.

2. Preliminary administration of prostigmin augments the response in many cases.

3. The effect is more marked when the P–R interval is initially 0.18 to 0.20 second than when it is less than 0.18 second.

4. The changes in conduction are maximal during the acute stages of carditis and tend to disappear as rheumatic activity subsides.

5. It is suggested that this procedure enhances the diagnostic value of prolongation of the P–R interval in rheumatic fever.

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THE PRIMARY INFLUENCE OF BASAL VASCULAR TONE ON THE DEVELOPMENT OF POSTOCCLUSIVE COLLATERAL CIRCULATION AND IN SELECTING PATIENTS FOR SYMPATHECTOMY

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While routinely determining the basal vascular tone* of patients with major peripheral arterial occlusions it became evident that the grade of the individual's general peripheral vascular tone played a decisive rôle in the development of a collateral circulation.

Despite general recognition of the importance of collateral circulation following a major peripheral arterial occlusion, very little is known of the factors determining its development. The present study offers objective evidence of a physiologic mechanism which operates to aid or to hinder the development of a collateral circulation in accordance with the individual's intrinsic vascular tone.

Although our observations are in contradiction to Lewis'[4] own concept of collateral circulation, we feel it is important to quote the following passages by him at length because they summarize so well the conflicting views on this subject:

"When a main artery to a limb becomes blocked, certain factors come into play, at once or after very short delay, and tend to restore the circulation to the distal tissue. As Recklinghausen pointed out there is, as a result of the obstruction, a little rise of pressure proximal to it, while there is a decided fall of pressure in the artery and its branches distal to it. These immediate changes in pressure increase the flow in branches issuing from the main artery proximal to the obstruction and supplying the territory in which the pressure

* Tone has been defined as the resistance muscle offers to stretch. This is analogous to our definition of vascular tone which is the ability of blood-vessels to constrict and to resist vasodilatation.

is lowered. Moreover, as Bier concluded, the vessels of the deprived territory will enter a state of reactive hyperæmia, owing as we should now say to the accumulation of vasodilator substances in the corresponding tissues.

"These early adjustments help to restore circulation. They are, however, inadequate to explain the formation of permanently enlarged channels. Thoma concluded on the basis of many observations that such growth of collateral channels occurs because blood flow through them is increased. In this he was supported by Nothnagel, who also expressed the view that the vascular growth is due to increased nutrition consequent upon increased flow through the vessel affected, or consequent upon increased flow through its vasa vasorum. It is to be noted that such collateral anastomoses develop whether the limb is previously deprived of nerves or not; the development is independent of nerve supply. Thoma's theory, that the growth or shrinkage of arteries is controlled by the amount of blood flowing through them, might be held adequately to explain the development of collateral channels when the main artery of a limb is obstructed."

In attempting to clarify the understanding of the mechanisms underlying the development of collateral circulation in general, Lewis drew upon his observations on arteriovenous fistulæ and further states:

". . . . and we are brought to ask if arterial growth is not directly controlled by a stimulant, a chemical stimulant arising locally as a product of the tissue need, and acting locally. The growth of collateral channels is so locally adjusted and occurs under such different circumstances of pressure and flow, that it now seems quite necessary to formulate an intimate and special mechanism to explain this permanent increase in size. The essence of the matter seems to be that there is a local call by tissues in need and that to this call there is a local and adequate response."

Lewis' concept, which is generally accepted,[6] does not seem entirely valid in view of our observations. If ischemia were the predominating stimulus for promoting a collateral circulation, individuals with high vascular tone with a major arterial occlusion, should develop a collateral circulation because of the severity of their ischemia, as in them there is certainly an intense "local call by tissues in need." Since they usually do not develop a collateral circulation, ischemia cannot be considered the principal stimulus to its development. We were finding that patients with a popliteal or femoral occlusion who had a low grade of vascular tone or relaxed peripheral vessels, as determined by the behavior of the vessels in the hands, almost invariably developed a collateral circulation, whereas similar patients with a high grade of vascular tone were very unlikely to develop their collaterals, and as a consequence their symptoms were much more severe.

Vascular tone tests have shown us that an individual's own particular grade of vascular tone, whether it be low tone or high, is the predominating influence on his ability to develop a collateral circulation. It may be that vascular tone acts, though in part only, in much the same manner as the mechanisms described by Thoma and Nothnagel. Their conclusions are, nevertheless, entirely inadequate to describe the conflicting responses in different patients with the same degree of arterial occlusion. At that time there was no objective method of measuring an individual's basal vascular tone, nor was the normal range known or considered as of primary importance in an individual

with a major peripheral arterial occlusion. It is only recently that it has been recognized that a constant gradient is maintained between the vascular tone in the hands and that in the feet. Consequently Nothnagel in 1889 and Thoma in 1896, though their observations were probably true in part, failed to account for the conflicting variety of responses in different patients with the same degree of peripheral arterial occlusion.

Our method of grading vascular tone is described in detail in a recent paper,[5] where 270 normals and patients were classified in 7 groups. For the purpose of this special study of collateral circulation it is sufficient to classify the patients into the two basic groups of high and low vascular tone, which can be determined by observations of the temperature responses in the hands alone. We regard an individual as having a high grade of vascular tone if the hands are cool (below 25° C.) 15 minutes after the patient has been in a constant temperature room at 20° C., unclothed except for a light gown. This individual's peripheral vessels are easily constricted. If, on the contrary, the hands remain warm (25° C. or above) after this same exposure, the patient is in a low vascular tone group. This individual's peripheral vessels are easily relaxed. For this test to be reliable the patient must be in a basal state at the start of the test, having omitted the preceding meal and any hot drinks, drugs, or hot bath that might induce vasodilatation. In cold weather (below 55° F.) subjects should be kept in a warm room for 30 minutes before starting the test. Since most of the patients discussed in this paper have occlusions of the major arteries of both legs, the toe temperatures were not considered when grading vascular tone, but were observed as the important indication of the presence or absence of collateral circulation.

In this study we determined the grade of vascular tone and its relationship to the incidence of collateral circulation and to the severity of symptoms in 70 patients with occlusions of the femoral or popliteal arteries. In 38 of the patients the occlusion was due to arteriosclerosis, in 30 it was due to thrombo-angiitis obliterans and in 2 due to embolism. Forty-four (63%) of the patients had a low grade of vascular tone and 26 (37%) had high vascular tone. Eighteen of the 30 patients with thrombo-angiitis obliterans had a low grade of vascular tone. Of the 38 patients with arteriosclerosis, 24 had a low grade of vascular tone.

Of the 44 patients with low vascular tone and with major occlusions, 38 (88%) had developed an excellent collateral circulation, some without any therapy. Of the remaining 12%, only 1 patient had an old occlusion. The others who did not have collaterals in this low tone group had a history of very recent occlusions. We have found clinically that some patients with bilateral occlusions had an adequate collateral circulation in the extremity with the oldest history of an occlusion, whereas the other leg with the recent occlusion had the inadequate blood flow of an undeveloped collateral circulation. It is our feeling that these patients in the low tone group will eventually establish an adequate collateral circulation in both extremities,

as have the great majority of the individuals with low vascular tone. Eckstein, Gregg and Pritchard[2] found that it took weeks for a complete collateral circulation to develop in experimental occlusion of the femoral arteries in dogs. Of the 26 patients with a high grade of vascular tone, only 9 (34%) had developed an adequate collateral circulation, and in half of these patients a posterior tibial nerve block with procaine was necessary before any dilatation of collaterals could occur.

We then reviewed the histories of these patients taken prior to this investigation, and recorded the incidence of severe symptoms (claudication at a half-block or less) and the presence or absence of gangrene or amputations. These findings were then related to the patients' grade of vascular tone. Whereas 17 of the 26 (65%) of the patients with high vascular tone had severe claudication, this was present in only 10 of the 44 (23%) of those with low vascular tone. A similar increase was found in the percentage of gangrene and amputations in the patients with a high grade of vascular tone.

These findings suggest that ischemia is not an effective stimulus in the development of a collateral circulation in patients with high vascular tone. In this investigation it appears that the grade of an individual's basal vascular tone plays the decisive rôle in encouraging or discouraging the development of a collateral circulation following a major peripheral arterial occlusion, probably because dilatation is the more frequent state of the collaterals in the individual with low vascular tone, and resistance to vasodilatation is the more frequent state in the individual with high vascular tone.

There was no correlation between the amount and type of therapy given to these patients and the development of a collateral circulation in the two vascular tone groups. Many with high vascular tone had treatment such as suction and pressure, the vaso-oscillating bed and forms of vasodilator therapy, including fever therapy, and yet had not developed a collateral circulation, though the elapsed time would have been sufficient for the development of collaterals in an individual with low vascular tone. Many of these patients whose basal vascular tone is high had their occlusions several years prior to this study. In the group with low vascular tone many had no therapy at all before they were seen by us, yet they had already developed collaterals. These findings explain why clinical results reported with new forms of therapy for peripheral vascular disease are so often unreliable. Until the natural course of an arterial occlusion is studied in individual patients by determining their vascular tone, one cannot attribute improvement to any form of therapy without the question arising as to whether or not improvement has been the spontaneous result of a combination of low vascular tone and the passage of sufficient time for the development of a collateral circulation.

The results of this analysis show that therapy, but not radical therapy, is indicated for the individual with low vascular tone with a major peripheral arterial occlusion. Often an instruction sheet on care of the feet is all that is necessary for these patients. If the occlu-

sion is recent, a short course of suction and pressure and mild vasodilator therapy is usually sufficient treatment until they have established an adequate collateral circulation. On the other hand, the patient with high vascular tone and no collateral circulation needs the benefit of the most intense and constant vasodilator therapy, often including sympathectomy.

When the striking difference in the natural course of major peripheral arterial occlusions was observed between the two groups of patients with low and high grades of vascular tone, we began recommending sympathetic ganglionectomy only in patients with a high grade of vascular tone. The wisdom of this method of selecting patients for sympathectomy was confirmed when we saw 2 patients with low vascular tone who had been sympathectomized prior to this investigation and who had an increase in the severity of their symptoms, probably as the result of too great a diversion of blood from the toes to vessels in the thigh and leg which had perhaps been dilated before the sympathectomy. Freeman and Montgomery,[3] in discussing lumbar sympathectomy in the treatment of intermittent claudication, describe an analogous situation. In 1 of the patients they discuss, following sympathectomy there was a marked increase in oscillations at the calf and a decrease in oscillations at the ankle after exercise, reflecting a diversion of blood from the foot. Atlas[1] has recently reported development of gangrene in 3 patients in whom lumbar sympathectomy had been done for peripheral arteriosclerotic disease. He believed that in these patients surgically induced relaxation of flexible arteriovenous anastomoses in an ischemic foot could shunt blood from the capillary bed in sufficient quantity to cause tissue necrosis and gangrene.

To us it seems irrational to sympathectomize an individual who has a low grade of vascular tone below the knee, since his collaterals are already in a state of vasodilatation or are in the process of developing, and one risks the hazard of diverting blood from the foot, the site where gangrene is most likely to develop. However, the patients with high vascular tone and whose symptoms are not improving or are becoming more severe deserve the benefit of immediate sympathectomy, regardless of whether the cause of the occlusion be thromboangiitis obliterans, arteriosclerosis or ligation of a major artery following injury. We now recommend sympathectomy in the latter group of patients, even though some have not vasodilated with procaine block of the posterior tibial nerve and the results have been uniformly good, with the exception of 1 patient who had a foot already in a hopeless state of gangrene when he was first studied.

By selecting the patients who are suitable for sympathectomy on the basis of their responses during the vascular tone test, the operation may find a more definite place in the treatment of arterial occlusive disease. Hitherto, patients who did not have a rise in toe temperature in response to a nerve block were not considered suitable candidates for sympathectomy because they lacked the capacity for vasodilation in response to procaine. Yet these patients are in the high vascular tone group who need sympathectomy most and who, in our experience,

are most benefited by the procedure. Sympathectomy in such cases, by creating a state of low tone of the arteries above the occlusion, encourages the establishment of a collateral circulation in the same manner as it occurs spontaneously in the individual with low vascular tone. In these patients, sympathectomy not only lowers the tone of the vessels above an occlusion and thereby increases the pressure stimulus for opening the collateral vessels, but at the same time lowers the tone of the collateral vessels themselves.

Conclusions. 1. An objective method is described by which, for the first time to our knowledge, one can predict whether a collateral circulation is likely to develop following a major peripheral arterial occlusion and whether a sympathetic ganglionectomy is indicated.

2. By determining the patient's basal vascular tone, which can be obtained from any unoccluded extremity, we are able to predict far more accurately the course of the disease, and to decide the amount and type of treatment required.

3. Patients who have a low grade of vascular tone will develop a collateral circulation almost invariably and, as a rule, do not require much active treatment.

4. The majority of patients who have a high grade of vascular tone do not develop a collateral circulation; and, since their symptoms are much more severe, require intensive treatment.

5. Only patients with a high grade of vascular tone require sympathetic ganglionectomy.

6. The previous method for selecting patients for sympathectomy on the basis of their capacity to vasodilate in response to paravertebral or local nerve block is erroneous. The patients who are in most urgent need for sympathectomy are those with high basal vascular tone who do not respond to temporary nerve block.

7. Patients with low vascular tone are not improved by sympathetic ganglionectomy.

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A FATAL CASE OF CEREBRAL COCCIDIOIDOMYCOSIS WITH CULTURAL STUDIES

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Coccidioidomycosis is a respiratory infection, usually self-limited, that follows inhalation of the chlamydospores of *Coccidioides immitis*. About 5% of the patients develop a toxic rash 2 or 3 days after onset,

followed by an erythema nodosum[14] often associated with polyarthritis. The disease is endemic in south central California, particularly the San Joaquin Valley, the southern half of Arizona, and western Texas. Several reviews of the literature on pulmonary coccidioidomycosis have appeared recently,[11,12,17] for the disease has become of increasing importance since large numbers of troops have been stationed in these areas.

In about 0.05% of cases[8] the pulmonary manifestations are followed by widespread hematogenous dissemination of the fungus. Miliary tubercles and confluent areas of caseation necrosis have been found in all of the visceral organs, the skin, joints,[12] and meninges of the brain and spinal cord. This generalized infection, called coccidioidal granuloma, is the only form in which the disease was known to medicine for over 40 years. Not until the publication of Dickson's paper in 1937[7] was it recognized that this illness, which carries a mortality of 50%, is an uncommon complication of the benign respiratory disease locally known as "San Joaquin fever."

In 1936 Abbott and Cutler[1] reviewed the literature of central nervous system coccidioidomycosis and found reports of 23 cases to which they added 11 of their own. The most common lesion was a basilar meningitis. In 2 instances there was an associated small intracerebral granuloma; in the first it was located in the right cerebral hemisphere, in the second a 4 mm. nodule was found in the right optic thalamus. Courville and Abbott[5] reported 5 additional cases of meningitis in 1 of which there was also a "small area of involvement of the superficial cortex." These authors point out that coccidioidal granuloma very rarely results in lesions within the nervous tissue itself. This is quite remarkable in view of the great frequency of meningitis (25%) in cases of disseminated coccidioidomycosis. A 4th case with a cerebral lesion was reported by Craig and Dockerty[6] who describe a granuloma 1 cm. in diameter in the left cerebellar hemisphere.

At the Army Institute of Pathology in Washington there are, at the time of writing, records of 23 autopsied cases of coccidioidomycosis in which the brain and meninges had been examined. With the exception of a male civilian, all were soldiers stationed in endemic areas during and after 1941. A basilar meningitis was found in 13 instances. In one of these there was an associated direct extension of the lesion into the underlying brain substance; in another a miliary granuloma in the substantia nigra (Cases 12 and 13, Table 1). Two cases (Cases 14 and 15) had intracerebral lesions without an accompanying meningitis. Equal numbers of white and Negro soldiers showed central nervous system involvement. This should not be interpreted as contrary to the accepted opinion that the disseminated form of coccidioidomycosis is much more common in the colored races, since the number of white troops stationed in endemic areas far exceeds that of Negro troops.

The rarity of invasion of nervous tissue by *C. immitis* when compared with its relatively high incidence of meningitis is in marked contrast to the lesions seen in blastomycosis where granulomata are

TABLE I.—OBSERVATIONS IN 15 CASES OF COCCIDIOIDOMYCOSIS WITH INTRACRANIAL LESIONS

Case No.	A.M.M.* Acc. No.	Age	Race	Systemic involvement	Duration of infection (mos.)	Duration of meningeal symptoms (mos.)	Spinal fluid findings	Leptomeninges	Brain
1	68315	32	B	Lungs	10	10	No record	Thickened at base and over cord	Normal
2	74661	40	W	D†	9	2	Wassermann 2+, WBC 2000, mostly lymphos; gold curve 5555544210	Fibrinous exudate and fibrous adhesions about base	Normal
3	77804	35	Y	Lungs	10	1	WBC 200, neutrophils 28%, lymphos. 72%; gold curve 2355432100	White granules about base of cbr., cbl. and parietal lobes	Normal
4	78078	35	W	D	4½	2	WBC 440, neutrophils 66%, lymphos. 34%, gold curve 5555432000	Thickened about base; few small nodules over parietal lobes	Normal
5	90363	35	B	Lungs mediast. ly. nodes	6	3	WBC 300, neutrophils 20%, lymphos. 80%, gold curve 2225422100	Fibrinous plaques at base	Normal
6	92498	21	W	Lungs	5	5	WBC 692, neutrophils 7%, lymphos. 93%, gold curve 5555554331	Thickened about base and over cord	Normal
7	97165	27	W	D	2	2	WBC 340, neutrophils 40%, lymphocytes 60%	Pale yellow gelatinous exudate about base	Normal
8	97521	31	B	D	2½	¾	No record	Thickened and granular about base	Normal
9	104135	37	W	None	6½	6½	WBC 690, neutrophils 13%, lymphos. 87%	Fibrinous, granular exudate about base	Normal
10	105308	27	B	D	2½	½	WBC 50, gold curve 0002422-200	Small granulomata seen micr. grossly normal	Normal
11	108221	24	W	D	2½	2½	WBC 650, neutrophils 65%, lymphos. 35%	Firm granular exudate about base	Normal
12	85443	22	W	D	4	1¼	Normal (early in disease)	Sl. thickening at base	Mil. lesion in substantia nigra
13	98017	25	B	D	3½	3½	WBC 900, neutrophils 60%, lymphos. 40%, gold curve 5555554300	Fibrous and fibrinous adhesions about base	Extension from meninges into brain
14	95409	23	B	D	3	None	Clear at autopsy	Normal	In medulla is a single spherule surrounded by lymphos. and neutrophils
15	114420	21	B	D	3	None	No record	Normal	Mil. nodules scattered through cbr., medulla and cbl.

* Army Institute of Pathology, Army Medical Museum, Washington, D. C.

† D = Disseminated.

characteristically found within the brain, and basilar meningitis is uncommon. The lesions of disseminated coccidioidomycosis are comparable to those of miliary tuberculosis, in which intracerebral granulomata are also very unusual. In fact, both the primary and the disseminated forms of coccidioidomycosis have much in common with the clinical picture and pathology of tuberculosis.[15] The miliary tubercle and caseous nodule of both diseases can be distinguished histologically only by discovery of the causative organism.

The case reported here is of interest for the unusually extensive intracerebral involvement following miliary spread of the organism.

Case Report.* The patient was a male of Italian parentage, 21 years old at the time of his induction into the Army in November, 1942. The family and early personal histories are essentially negative. From April to September, 1943 he was in the Arizona desert, 100 miles west of Phoenix. During June and July he went on maneuvers for 3 weeks in the desert regions of southern California. About September 1 he developed pain in his chest and a dry nonproductive cough which later was associated with expectoration of sticky colorless mucus. At about this time the patient first noticed a small papule behind his right ear. The lesion slowly increased to 1 cm. in diameter while the surface became ulcerated and discharged pus. Early in October he began having frequent drenching night sweats, not accompanied by any marked loss in weight.

On October 20, 1943, he was admitted to a station hospital where the granulomatous lesion behind the right ear was noted, as well as an enlargement of the adjoining cervical lymph nodes and bilateral supraclavicular lymphadenopathy. A Roentgen ray of the chest showed clear lung fields and widening of the mediastinum. Microscopic examination of the sputum and of the pus from the skin lesion revealed the spherules of *Coccidioides immitis*. Skin tests with coccidioidin were negative in dilutions of 1:1000 and 1:100. This is a not infrequent finding in disseminated coccidioidomycosis,[13] in contrast to the positive reactions almost invariably found accompanying the primary pulmonary lesion. The serum complement-fixation test was positive (Stanford University School of Medicine) in a titer of 1:64. This was interpreted by Dr. C. E. Smith as evidence of dissemination.

When admitted to this general hospital in November, 1943 the patient still appeared well nourished and complained only of cough, occasional blurring of vision, and a feeling of weakness. However, he had a daily rise in temperature to 101° F. and his general condition gradually declined. During the course of his illness many scattered granulomata appeared on the skin. These usually drained for several weeks but eventually healed. Lymphadenopathy often ended in abscess formation, the spherules of *C. immitis* being recovered from the pus.

Early in January, 1944 headache, of which he had previously rarely complained, became persistent and was associated with progressive amblyopia and diplopia. In May the signs and symptoms of bilateral III nerve paralysis were more pronounced and were accompanied by loss of the power of accomodation. At this time vomiting also set in and he became quite drowsy, though it was possible to rouse him. By the end of June this had deepened into stupor and for weeks before death on July 24, 1944, he was comatose.

Laboratory Findings. On admission the red cell count was 4,590,000, hemoglobin 90%, leukocytes 15,300 (neutrophils 70%, lymphocytes 16%, eosinophils 3%, basophils 2%). Before death the number of erythrocytes fell to 3,000,000, leukocytes to 13,000. Spherules of *C. immitis* were frequently found in the sputum. The urinary findings were not significant. The Kahn and Wassermann tests were negative; the complement-fixation test for coccidioidal infection remained at the high titer of 1:64. Spinal fluid (1/18): leukocytes 0,

* Clinical data were made available through the courtesy of Major Arthur Heyman.

globulin 1+, colloidal gold curve 5543210000, no organisms. 6/25: leukocytes 120 (neutrophils 15%, lymphocytes 85%), globulin 4+, colloidal gold curve 5555555321, no organisms. Biopsy of the skin lesion showed a typical granuloma with foreign body giant cells containing the spherules of *C. immitis*.

Roentgen ray. The admission film showed a mass in the superior mediastinum, most pronounced on the right; the lung fields were clear. Subsequent chest films revealed a slight increase in width of the mediastinum. Skull, long bones, and pelvis were negative.

Therapy. While at the station hospital the patient received 2 immunotransfusions of blood from donors who had recovered from coccidioidomycosis. There was no evidence of any beneficial effect. Goldstein and McDonald[8] used this treatment in 2 patients who were critically ill with pulmonary consolidation and effusion due to infection with *C. immitis* and both showed immediate clinical improvement.

At this hospital, potassium iodide was administered, beginning with 10 minims t.i.d. The amount was gradually increased to 60 minims t.i.d. and was continued for 2 months without evidence of improvement. Intravenous injections of coccidioidal vaccine were given on alternate days beginning with 0.1 cc. of a 1:1000 dilution and increasing to 2 cc. of the undiluted vaccine. This amount was administered for 2 months, but no improvement was noted.

Two courses of penicillin therapy were given. During the first, from March 17 to April 11, 3,120,000 Oxford units were administered intramuscularly in quantities of 15,000 units every 3 hours. In the second course, from May 22 to June 21, a total of 3,720,000 Oxford units were similarly injected. Although the skin lesions appeared smaller, this was due to disappearance of the secondary hemolytic staphylococcic infection, rather than to any effect upon the fungus. The failure on the part of penicillin to inhibit the growth of *C. immitis* is in striking contrast to the results obtained with 3 cases of actinomycosis of the jaw treated in this hospital. After 3 to 4 weeks of penicillin therapy the lesions healed and have remained so without recurrence for periods of 7 months to a year.

Autopsy. The body was that of an emaciated 22 year old white male. Near the base of the neck on the right side were 2 shallow ulcerations each 1.5 cm. in length. Behind the left ear and on the left side of the neck were similar lesions covered by a thin crust and measuring 3 mm. in diameter. The first interphalangeal joint of the right middle finger was swollen and fluctuant. Axillary lymphadenopathy was most marked on the right. Beneath the right pectoral muscles was an irregular 3 x 5 x 7 cm. abscess cavity filled with viscid yellow-brown pus, which on culture yielded a pure growth of *C. immitis*.

The peritoneum was thin and glistening, no free fluid was present, and the normal visceral relations were preserved. The serosal surfaces of the pericardium were smooth, the sac contained 10 cc. of clear yellow fluid. The pleuræ were transparent, no adhesions or free fluid were present. The mediastinal and hilar lymph nodes were enlarged, matted together, and on section had a speckled appearance due to many orange-yellow areas of focal necrosis. The para-aortic and mesenteric lymph nodes were likewise enlarged, some reaching a length of 2 cm. Histologically, they had lost all trace of their normal architecture. Small islands of lymphoid tissue were scattered through masses of granular pink staining material containing the spherules of *C. immitis* in large numbers.

The lungs were grossly normal. Microscopic examination revealed several small collections of lymphocytes and multinucleate foreign body giant cells. Only rarely was a spherule of *C. immitis* seen in these lesions, although in the adjacent lymph node they were very numerous. Many of the bronchioles were filled with neutrophils, others contained necrotic material in which were many spherules.

The heart weighed 280 gm.; gross and microscopic examination failed to reveal any abnormalities. The spleen, which weighed 140 gm., was likewise

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grossly normal. Histologically, there were several miliary tubercles, though no spherules could be found.

The entire gastro-intestinal tract, including the liver, gall bladder, and pancreas, was grossly normal. Only in the liver did histologic examination show occasional scattered coccidioidal granulomata.

Both kidneys were of normal size, shape, and consistency. The capsule stripped with some difficulty, although the underlying surface was smooth, dark red in color. On the surface of the left kidney was an irregular, poorly defined, yellow-white discoloration which on section was seen to extend a short distance into the cortex. The majority of the papillæ in each kidney bore irregular partly confluent 2 mm. areas of caseation necrosis. Microscopically, the glomeruli and tubular epithelium were intact. Scattered through the parenchyma of both cortex and medulla were numerous granulomata consisting of epithelioid cells, lymphocytes, plasma cells, and occasional foreign body giant cells some of which contained the spherules of *C. immitis*. The ureters, bladder, prostate, and testes were normal.

The left adrenal appeared normal; but the right was greatly enlarged, measuring 5 x 4 x 3 cm. On section a firm yellow-white mass was seen replacing most of the medulla. Histologically both cortex and medulla were found to be involved; much of the normal tissue was destroyed and replaced by a pink staining granular material containing countless spherules of *C. immitis*. About the margins of the necrotic areas were foci of granulation tissue.

The brain weighed 1580 gm., the convolutions were of normal complexity though somewhat flattened. About the base, and most dense at the optic chiasm, was a firm, gray, translucent exudate. Section through the midbrain revealed a central, 1.5 cm. spherical yellow-green mass replacing the normal tissue (Fig. 1). It extended posteriorly to involve the cephalic portion of the pons, and anteriorly into the mesencephalon where it infiltrated the tegmentum and pulvinar on the left. The cerebral aqueduct was not compressed. At the level of the optic chiasm the meningeal exudate infiltrated the nervous tissue about both optic tracts and extended into the hypothalamus. A firm 1.5 cm. nodule was present on the floor of the left lateral ventricle in the region of the caudate nucleus. Similar lesions averaging 5 mm. in diameter were scattered through the cortical and subcortical areas of the parietal and temporal lobes. In the right cerebellar hemisphere at the cortico-medullary junction were 2 discrete 1.3 cm. gray-green nodules (Fig. 2). A similar lesion, 5 mm. in diameter, was present in the left cerebellar hemisphere.

On histologic examination, many granulomata containing spherules of *C. immitis* were found in the subarachnoid space. In several areas the underlying cerebral cortex had been invaded by direct extension. However, the lesions of the cerebellum, the mid-brain, the lateral ventricle, and the smaller foci scattered through the cerebral hemispheres (Fig. 3), were apparently due to hematogenous distribution of the fungus.

In whatever tissues they were found, the spherules of *C. immitis* were surrounded by granulation tissue which closely resembled that seen in tuberculosis. The organisms averaged 20 to 30 micra in diameter, though when recently liberated as endospores they were only 3 micra in width. The wall, which was about 1 micron thick, consisted of two layers—an inner one that stained with eosin, and an outer highly refractile colorless membrane. The content of the spherules was basophilic and often vacuolated. Many were empty; in others the inner mass was subdivided into smaller bodies which, in the more mature stages, had rounded up to form the characteristic endospores. No mycelial threads were seen.

Cultural Studies. The spherules found in the sputum, pus, or tissues of the infected man or animal are generally thought to represent the parasitic phase in the life cycle of *C. immitis*. This phase consists in the growth of the spherule and the maturation of its endospores. The spherule finally ruptures and the endospores pass into the tissues, there in turn to become spherules and liberate a new generation of endospores. When spherules are placed on culture media, hyphæ grow out from them to form a mycelium in which some of the cells

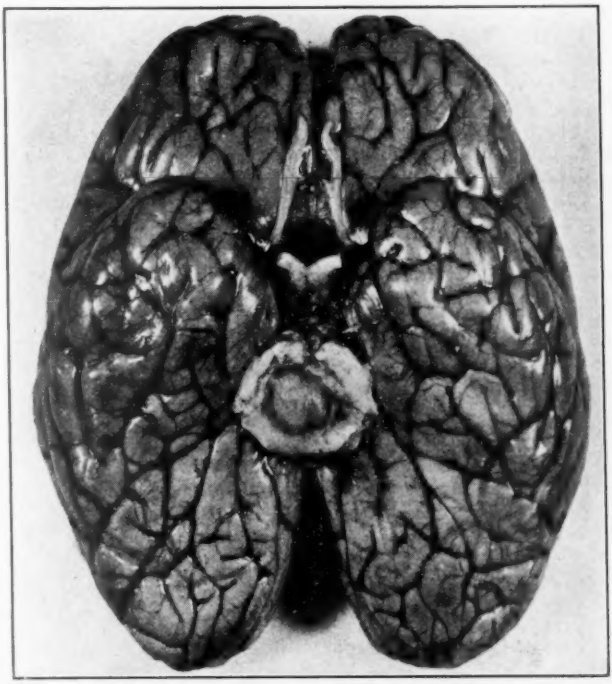

FIG. 1.—Ventral surface of brain. The cerebellum has been removed, the section passes through the midbrain just anterior to the pons. In the center of the cut surface is a circular 1.5 cm. granuloma. About the optic chiasm is a heavy gray translucent exudate.

FIG. 2.—Vertical section through the right cerebellar hemisphere. At the corticomedullary junction of the ventral aspect are two circular granulomata. One of these is well circumscribed, the other is infiltrating the surrounding tissue.

enlarge to form reproductive bodies known as chlamydospores. Until recently, spherule formation had not been observed in this, the so-called saprophytic phase of the life cycle of the fungus.

In 1914, MacNeal and Taylor[10] inoculated fresh pus into tall tubes of ascitic fluid or gelatinized horse serum containing a piece of sterile rabbit kidney. A mycelium did not develop when these tubes were kept in an atmosphere of hydrogen, but the spherules originally present in the pus continued to multiply, occasionally for as long as 3 weeks. Lack,[9] in 1938, used Hall tubes which he filled with neutral glucose broth to well above the point of constriction. The inoculum of chlamydospores suspended in egg albumen was pipetted into the tube and the constriction sealed off with a sterile marble. Gentle heating then partly coagulated the medium. Spherules appeared after about 7 days; the growth of hyphæ was completely inhibited.

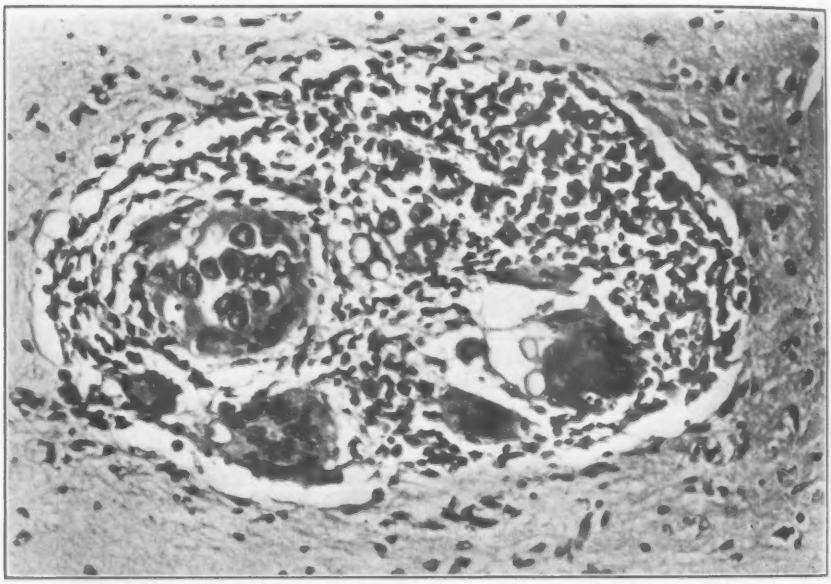

FIG. 3.—Miliary granuloma in the cerebral cortex. Four large foreign body giant cells are at the periphery, 3 contain spherules of *C. immitis*. Several spherules are present in the center of the lesion. The small cells are lymphocytes and plasma cells. (Hematox. eos. × 330.) (U. S. A. Med. Mus. Neg. No. 81998.)

In these investigations spherule formation occurred under conditions simulating those found in the animal body, and a mycelium failed to develop. They thus supported the view that the parasitic and saprophytic phases of the life cycle were separate and distinct. However, in 1941, Baker and Mrak[2] reported finding structures resembling spherules in 3 of 16 strains of old partially dried out agar cultures of *C. immitis*. Culture spherules were found after 1½ to 2 months incubation, when active growth of the fungus had ceased. They were never seen in liquid media. In a subsequent article[3] these authors point out that the discovery of spherules in cultures eliminates the need for postulating two independent phases in the life cycle of *C. immitis*. They state further that thus far culture spherules had been observed in only 4 strains, and constantly in only 1. It seemed desirable, therefore, to attempt the production of both mycelium and spherules in the same culture by somewhat different methods.

Technique. Sputum and pus obtained from this case were streaked on Sabouraud's agar and kept at room temperature. Mycelial growth in the form

of a loose, white, whorled cotton-like fluff appeared in all tubes after 5 days. Two weeks after inoculation many hyphæ had grown over the inner surface of the tube where no agar was present, facilitating microscopic examination. In some of these regions rectangular chlamydospores were found; spherules were never seen. Subcultures were made to agar plates for the purpose of studying colony formation (Fig. 4) and to eliminate any spherules that had been carried over in the original inoculum which might still be present in the culture.

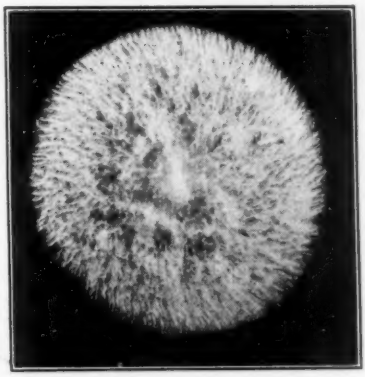

FIG. 4.—Mycelium of *C. immitis* 6 days after inoculation on Sabouraud's agar.

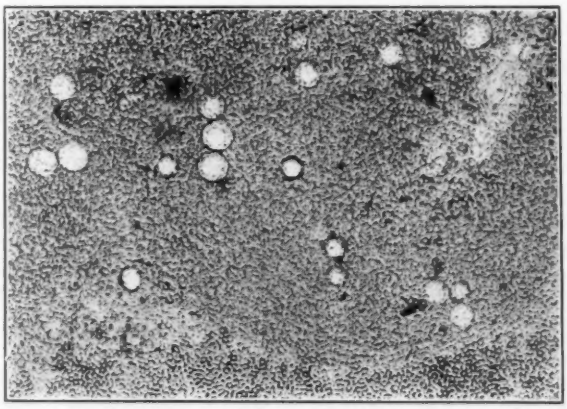

FIG. 5.—Growth of mycelium and spherules in citrated human blood kept in roller tube. The spherules are enmeshed in the mycelium which is obscured by erythrocytes. (Fresh preparation. × 80.)

Six or 7 days after subculture, bits of the mycelium were inoculated into test tubes containing 1.5 cc. of heparinized or citrated blood kept at 37.5° C. The tubes were placed in the roller tube apparatus designed by Gey and modified by Coman and Stabler[4] for use in tissue culture. Essentially this is a slowly revolving (9 r.p.h.) circular rack that carries about 50 tubes which lie on their sides, but are slightly tilted so that none of the blood will come in contact with the rubber stopper. The fungus grows on the inner surface of the tubes where it is bathed by the slowly circulating blood. If a tube is placed on the upward tilted stage of a microscope, and its bottom directed toward the observer, the blood will collect there, permitting examination of the fungus attached to the sides of the tube.

Experimental Observations. Twenty-four hours after inoculation, microscopic examination showed small islands of mycelium scattered over the inner surface of the tubes. During the next 3 days the colonies slowly increased

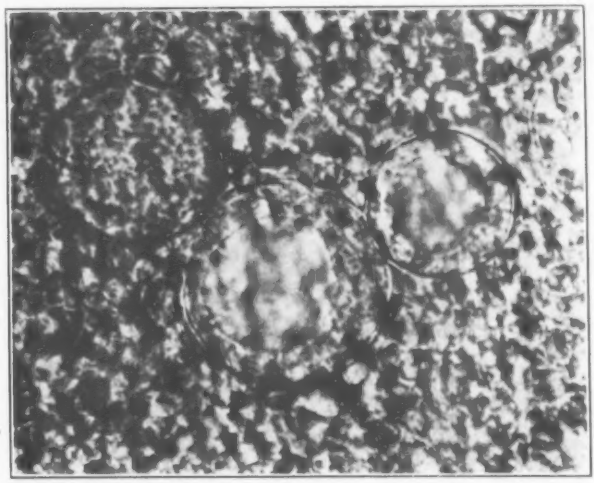

FIG. 6.—Three large spherules, 50 to 60 micra in diameter, growing in citrated blood within a roller tube. In 2 the cytoplasm surrounds a large central vacuole, in the third it completely fills the spherule. (Fresh preparation. × 450.)

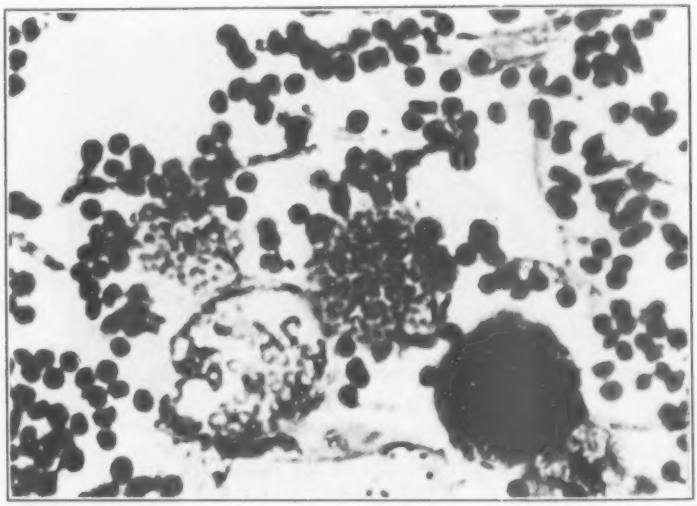

FIG. 7.—Section of mycelial mat grown in roller tube, showing 4 poorly defined spherules with their endospores. One spherule is almost empty, but still contains a few large endospores some of which are passing through a rent in the wall. The solid black disks scattered through the field are erythrocytes. (Hematox. eos. × 810.) (U. S. A. Med. Mus. Neg. No. 82000.)

in size, and spherules began to appear. These were often embedded in a mass of hyphæ (Fig. 5), but occasionally were wholly free of the mycelium. In some instances the cytoplasm formed a peripheral layer beneath the highly

refractile wall of the spherule and surrounded a large central vacuole (Fig. 6). When spherules were isolated and placed in a hanging drop of lactose broth, hyphæ grew from the endospores within 24 hours. Rarely this type of germination was also seen within the blood tubes. Though never observed in the living state, histologic sections of the mycelial mats removed from the tubes showed large endospores within and surrounding collapsed spherules (Fig. 7). This would indicate that spherule formation by the liberation of endospores was taking place.

Four to 5 days after inoculation, chlamydospores began to appear as localized swellings on the hyphæ. Some remained small and fusiform, others formed spherical structures which might be mistaken for culture spherules. However, the absence of endospores in the former and their presence in the latter is an aid to identification. Culture spherules in which no cleavage has taken place have a granular cytoplasm; that of chlamydospores is usually clear and almost hyaline. The development of spherules from chlamydospores noted by Lack[9] was not seen in these cultures, but its occurrence is not improbable. Degenerative changes began 10 to 14 days after inoculation. The cells of the mycelium became vacuolated, the hyphæ broke up into short lengths, the spherules disintegrated and disappeared.

Replacing air in the tubes with hydrogen had no apparent effect upon the development of the mycelium or spherules. Nor was growth altered by the kind of anticoagulant used, both heparinized and citrated blood proving satisfactory. If the tubes were placed on a slant, but not rotated, the erythrocytes settled out; some mycelial growth took place, but spherules were rarely found. To test the effect of rotation alone, brain heart infusion broth instead of blood was used. A mycelium formed, but no spherules developed. In serum a good growth of mycelium occurred with the production of many chlamydospores and a moderate number of spherules.

Animal Inoculation. Mycelium growing on Sabouraud's agar was suspended in 0.85% sodium chloride; 0.5 cc. was injected intraperitoneally into 4 mice, 2 hamsters, and 4 frogs. In 2 additional frogs, bits of mycelium were placed in the anterior chamber of one eye.

Mice. The mice, serving as a control series for the hamsters and frogs, were killed at intervals between 10 and 32 days after inoculation. In all, the spleen and mesenteric lymph nodes were moderately enlarged. Several 1 mm. yellow-white nodules were scattered through the liver and both lungs. Histologic examination showed the characteristic granuloma containing many spherules of *C. immitis.*

Hamsters. The first animal died 10 days after inoculation, the second was killed on the following day. The lungs were riddled with confluent 1 to 3 mm. white nodules (Fig. 8). Similar lesions, but more discrete, were present in the liver and spleen. The mesenteric lymph nodes were enlarged and matted together. Microscopically the typical granulomata consisting of lymphocytes, epithelioid cells, and foreign body giant cells were seen. The spherules were often very large; occasionally one was found that had ruptured, the liberated endospores infiltrating the surrounding tissue (Fig. 9). In view of the presence of coccidioidomycosis in wild rodents of regions in which the disease is endemic,[16] the susceptibility of the hamster to the fungus was not unexpected.

Frogs. These animals were inoculated to determine if the fungus when introduced into a cold blooded animal would grow, and if it did, whether as a mycelium or by endosporulation. The first frog died 3 days after inoculation. Death was due to an intercurrent infection, the so-called "red leg." Flakes of fibrinous exudate were attached to the surface of the bladder, stomach, spleen, and liver. Histologically the lesions consisted of fibrin, enmeshed in which were many eosinophils, basophils, and lymphocytes. Scattered among them were many short hyphal fragments, the cells of some of which had rounded up to form small spherical chlamydospores.

A second frog was killed 8 days after inoculation. On the peritoneal surface near the site of inoculation were two yellow-white nodules, each 2 mm. in diameter. A 2.5 mm. nodule was present in the region of the pancreas, and

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two smaller ones were on the surface of the bladder. Many 0.3 mm. tubercles were found in the mesentery. Histologically the lesions consisted of connective tissue infiltrated by many eosinophils, macrophages, and lymphocytes. Many small spherules, most of which showed only a single cleavage plane, were found within the cytoplasm of the macrophages. Occasionally one or two cell

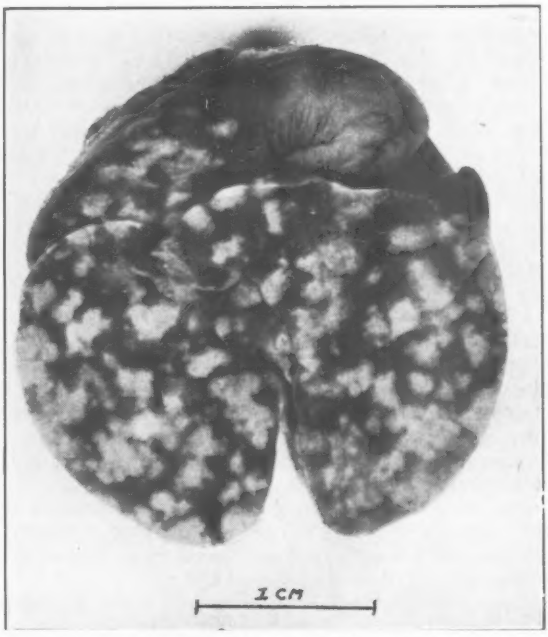

FIG. 8.—Heart and lungs of a hamster that died 10 days after intraperitoneal inoculation with the mycelium of *C. immitis*.

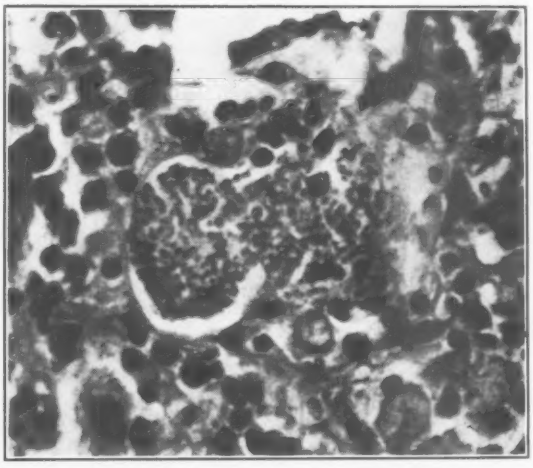

FIG. 9.—Section of the spleen of hamster shown in previous figure. A large spherule has ruptured and the endospores are escaping into the adjacent tissue. (Hematox. eos. × 450.)

lengths of degenerating mycelium were also found; most had been phagocytized. Foreign body giant cells were almost wholly absent. When bits of the tissue were placed on Sabouraud's agar, growth of the fungus was apparent after 2 days. The remaining animals were killed 18 days after inoculation. In both only a few 0.1 mm. fibrous granules were found on the peritoneum near the site of injection.

To enhance the possibility of hyphal growth, bits of mycelium were placed in the anterior chamber of one eye in each of 2 frogs. After 2 weeks the cornea was hazy, but the mycelium had disappeared. Histologically, small granulomata were found in the cornea and iris similar to those seen on the peritoneal surfaces of the other animals. There had been no growth of the mycelium.

Discussion. The course of the patient's illness was quite typical of that usually seen in disseminated coccidioidomycosis. The onset of symptoms with cough indicates that the primary lesion was in the lungs. Yet, though spherules of *C. immitis* were often found in the sputum, the lung fields were clear on Roentgen ray, and gross lesions were not found at autopsy. Mediastinal lymphadenopathy associated with minimal pulmonary involvement, as demonstrated in this case, is a frequent finding in the generalized disease.

The first evidence of an intracranial lesion was occasional blurring of vision noted by the patient 8 months before death. His ability to survive for so long after involvement of the central nervous system probably accounts for the massive character of the lesion found there. However, even shortly before death the fungus could not be isolated from the spinal fluid. This is also true of the 15 cases listed in Table 1.

The presence of numerous spherules in association with an actively growing mycelium in the roller tubes lends support to the contention of Baker and Mrak that the parasitic and saprophytic life cycles of *C. immitis* are not wholly separate and distinct; that they may occasionally occur simultaneously. A marked difference in these two phases of the life cycle of a number of pathogenic fungi has long been recognized. Using the roller tube technique and heparinized blood as a culture medium, one of these, namely *Histoplasma capsulatum*, was studied along with *C. immitis*. Here also both the mycelium and yeast-like form grew in the same culture tube.

Since it was now possible to grow the mycelium and spherules of *C. immitis* in the same culture as saprophytes, the next step would be to find both in animals as parasites. The hamster proved very susceptible to infection with the fungus, but only spherules were found in the lesions. Frogs were used in the hope that these animals, with their lower body temperature, would provide a more favorable environment for the mycelium, particularly if the latter were placed in the anterior chamber of an eye. However, no growth of the mycelium occurred and the spherules that developed only reached the two-cell stage. The granulomata found in the peritoneum and cornea were in the nature of a non-specific foreign body reaction.

Summary. A fatal case of disseminated coccidioidomycosis is reported in which the outstanding lesions were found in the brain. Fifteen additional examples of intracranial infection by the fungus are listed. The organism was isolated and both mycelium and spherules

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grown in culture using the roller tube apparatus of Gey. Hamsters were very susceptible to the fungus, frogs were refractory. Neither in the patient nor in the experimental animals was there evidence of mycelial growth.

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PNEUMOCOCCIC PNEUMONIA RESEMBLING PRIMARY ATYPICAL PNEUMONIA

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During the past few years much emphasis has been placed both by clinicians and laboratory workers on "primary atypical pneumonia, etiology unknown." This designation was suggested by the Commission on Pneumonia†[7] in place of the variety of terms that have been applied to this clinical syndrome. Many agents have been suggested as playing a rôle in its etiology. Clinical similarity to the proved virus pneumonias of the ornithosis group, epidemiologic studies, the negative bacteriologic results and the resistance to sulfonamide treatment have greatly contributed to the concept that this disease is due to a virus infection. However, it has been repeatedly stressed[4,5] that pneumonias of non-viral origin, such as coccidioidomycosis,[2] Q-fever,[1] and so on, can give a very similar clinical picture.§

Study of patients admitted to the Pneumonia Service of Harlem Hospital has impressed us with the not infrequent occurrence of cases of proved pneumococcic pneumonia with a picture closely resembling

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† A Board for the investigation and control of influenza and other epidemic diseases in the United States Army.

§ Dr. H. A. Reimann has recently suggested that these be called "viroid" pneumonias. As he suggests, there is ample precedent for such a word, which also can better cope with atypical instances than could "atypical atypical pneumonia."—Editor.

primary atypical pneumonia. The insidious onset, patchy infiltration of the lung, scanty sputum with a hacking cough, relative bradycardia together with the Roentgen ray findings, have often led us to a tentative diagnosis of primary atypical pneumonia. The occurrence of positive blood cultures or the occasional appearance of complications such as a pneumococcic empyema, has made us more cautious in our clinical diagnosis of sporadic cases of primary atypical pneumonia. It is quite possible that the pneumococcic pneumonia may have been superimposed on a primary virus infection. However, the striking response in these patients to specific serum therapy and the increasing occurrence of sulfonamide-fast strains warranted further investigation.

In this paper, a study of cases of pneumococcic pneumonia in adults admitted to Harlem Hospital during the 4-year period (1939 to 1943) is reported, with special reference to atypical forms and their response to chemotherapy and specific serum treatment.

Method. The procedure adhered to by the Pneumonia Service at Harlem Hospital, in arriving at an etiologic diagnosis and the selection of proper therapy was as follows:

Immediately following admission, a complete history was obtained and physical examination carried out. Sputum was collected for typing and blood drawn for culture and initial immunologic studies (type specific agglutinins, precipitins and C-reactive protein). A Roentgen ray of the chest was taken as a routine. The patient was given chemotherapy as soon as the diagnosis of pneumonia wa made. (Sulfadiazine, 4 gm. stat. and 1 gm. every 4 hours.)

Sputum was typed directly by the Neufeld method and after intraperitoneal mouse inoculation. Intraperitoneal fluid as well as mouse brain cultures were studied within the next 24 hours. If pathogenic organisms were not found, additional samples of sputum were examined.

The patient with characteristic pneumococcic pneumonia usually showed a response to chemotherapy by the time the sputum was typed. In the event that a response did not occur, despite an effective blood sulfonamide concentration, the isolated organisms were tested *in vitro* for fastness, and the patient's serum tested for sulfonamide inhibitors according to the method of MacLeod.[6] If the organism was fast to all of the sulfonamides and the patient still failed to respond, serum therapy was instituted promptly.

In some patients repeated examination of the sputum yielded no suspected pathogens. Under these circumstances another procedure was employed in an attempt to obtain a bacteriologic diagnosis. For this purpose a method which we have termed "reverse" typing was used. A sample of serum was obtained from the patient every 2nd day and was tested against 56 stock strains of pneumococci for "quellung" reaction. In the average case of pneumococcic pneumonia, after 5 to 7 days the patient had developed a sufficiently high concentration of antibodies to produce distinct capsular swelling with the homologous type pneumococcus. Details of the procedure are reported elsewhere.[10]

Case Reports. Some illustrative cases are here reported.

CASE 1. *Atypical pneumococcic pneumonia without response to chemotherapy.* H. S., aged 42, was admitted with a 3-day history of cough, fever, chills, night sweats and pain in the left chest. The temperature was 104° F., with a relative bradycardia throughout the course. The W.B.C. on admission was 2150 and 1 week later 16,750. There was slight dullness with râles over the right lower lobe. Serial Roentgen rays revealed migrating pneumonia involving right lower lobe, right middle lobe and then the left lower lobe. Type XII

pneumococcus was found in the sputum, mouse peritoneal fluid and mouse brain. Test for C-reactive protein was positive and agglutinins for Type XII appeared in rising titer during the course. The temperature was spiking for 4½ weeks in spite of 2 courses of sulfonamide therapy. There was no evidence of complications. There was a return to normal by lysis and the patient was discharged after 5 weeks, asymptomatic.

Comment. This case is cited as a suggestive example of a primary virus infection followed by a secondary invasion by a bacterial organism. The patchy migrating pneumonia, the relative bradycardia, leukopenia and the lack of response to chemotherapy resemble the picture seen in primary atypical pneumonia. The secondary rise in leukocytes with the appearance of specific antibodies indicate that pneumococcus XII was a secondary invader. As pointed out later, we and others have observed repeatedly the ineffectiveness of sulfonamides and the apparent superiority of specific serum therapy in treating infections caused by this type of pneumococcus. (See Table 2.) The prolonged course as seen in this patient occurs often in cases with migrating and bilateral pneumonia, although in our experience, this is very rare in pneumococcus Type XII pneumonia.* (See Table 1.)

CASE 2. *Atypical pneumococcic pneumonia with response to chemotherapy.*

J. P., aged 55, was admitted with a history of insidious onset of cough, substernal ache, fever and chills. The temperature was 103° F. with a relative bradycardia. There was slight dullness with numerous fine râles over both lower lobes. Roentgen ray revealed bilateral infiltration of the lower lobes. The W.B.C. was 11,000. Type III pneumococcus was found in the sputum and mouse peritoneum. Positive agglutinins for Type III appeared irregularly. Sulfadiazine produced a response and then was discontinued. On the 12th day, the temperature rose to 102° F. and sulfadiazine was reinstituted with prompt response and recovery.

Comment. In our experience, patients with pneumonia caused by pneumococcus Type III have shown, frequently, absence of demonstrable antibodies from their serum. With daily examination, antibodies are found to appear and disappear from the blood stream, and can be easily missed if only a single examination is made. The presence of large numbers of pneumococcus Type III in the sputum and the response to sulfonamide therapy indicate that Type III was etiologic in this case. Not infrequently, relatively large amounts of free SSS III can be found in the serum in the early stages of the disease, which establishes the etiology and at the same time may partially explain the lack of demonstrable antibodies.

CASE 3. *Atypical pneumococcic pneumonia with response to serum.*

E. W., aged 80, was admitted with a 2-week history of cough, headache, chilly sensations and fever. The temperature was 102° F. with a relative bradycardia. There was diminution of breath sounds with râles in both lower lobes. Roentgen ray examination revealed patchy infiltration of both lower lobes. Type XVIII pneumococcus was found in the sputum, mouse peritoneum and mouse brain cultures. On the 2nd day of hospitalization, the temperature was 104.2° F. Rabbit serum (Lederle), Type XVIII (142,500 units) was given. The patient recovered.

Comment. This patient presented a picture characteristic of primary atypical pneumonia. The patient's niece, however, was ill at the same time with classical pneumococcic pneumonia caused by the same type of pneumococcus. The patient's response to serum therapy was no less striking than the effectiveness of the sulfonamide therapy in the niece.

CASE 4. *Atypical pneumococcic pneumonia with high titer of cold hemagglutinins.*

S. J., a 30 year old colored male was admitted to the hospital with a temperature of 102° F., pulse 92, respiration 16. He gave a history of chilly sensations with non-productive cough the day before admission. He did not

* This case was admitted to Harlem Hospital after March 1, 1943, and is not included in Tables 1 and 2.

appear acutely ill. Physical examination revealed râles over the left lower chest with no signs of consolidation. The Roentgen ray department reported bronchopneumonia in the left lower lobe. Next morning his temperature rose to 103.4° F. and continued to spike between 101° and 104° F. There was marked relative bradycardia throughout the period of 9 days of high temperature. The W.B.C. was 7950. A Type XXI pneumococcus was recovered from the sputum. Sulfadiazine (23 gm.) was ineffective. During the first 10 days of the disease there were no agglutinins in the patient's serum for Type XXI pneumococcus. Then the type specific agglutinins appeared and rose to a titer of 1:64 (2+) 2 weeks after onset of the disease. Cold agglutinins which were absent at the onset appeared on the 7th day and rose to a titer of 1:2000. Absorption of the Type XXI agglutinins by the homologous pneumococci did not change the titer for cold agglutinins in the serum.

CASE 5. *Atypical pneumococcic pneumonia with high titer of cold hemagglutinins.*

G. S., a 32 year old white male, gave a history of an upper respiratory infection for 2 weeks prior to admission. He was treated by his local physician for 5 days with sulfadiazine without response. The diagnosis at this time was pneumonia of the left lower lobe. The patient was restless, dyspneic and developed erythema over the abdomen. The sulfonamide was discontinued and the patient began to show some improvement. However, after a few days he started to cough again and was sent to the hospital. Roentgen ray on admission showed peribronchial infiltration in the left lower and right upper lobes. The temperature was 103° F.; pulse 100; respiration 32. Next morning his temperature went up to 105° F. and then gradually fell to normal after 7 days. Type XXXIII pneumococci were recovered from the sputum and a high titer of homologous agglutinins were found in his serum. At the same time cold agglutinins in a titer of 1:16,000 were present in the patient's serum.

Comment (Cases 4 and 5). In view of the report of cold agglutinins[9] in primary atypical pneumonia, these 2 cases are of special interest. Cold hemagglutinins are usually not found in pneumococcic pneumonia in high titers. Thomas *et al.*[11] have reported cold hemagglutinins in a large number of primary atypical pneumonias where simultaneously agglutinins for an indifferent streptococcus were found. They also observed the same titer of cold agglutinins after absorption of the streptococcic agglutinins from the convalescent serum.

Collected Data. In hospital and private practice, the Roentgen ray findings and failure to respond to chemotherapy have been most commonly used as the outstanding objective criteria in the diagnosis of sporadic cases of primary atypical pneumonia. To evaluate these 2 criteria, tables of their frequency in pneumococcic pneumonia were prepared. Table 1 represents the occurrence of bilateral patchy infiltration in pneumococcic pneumonia, and Table 2 the response to chemotherapy of pneumonia patients with either typical or atypical Roentgen ray findings. Most of the common pneumococcal types are represented. Some of the higher types were chosen at random.

Comment on Table 1. Bilateral patchy infiltration has been claimed to be one of the characteristic findings in primary atypical pneumonia. It can be seen from Table 1 that the incidence of bilateral involvement for most types is about 10%. These lesions usually were patchy, while the unilateral lesions were, in general, a dense lobar consolidation. Even in the latter group, however, a patchy bronchopneumonic infiltration was encountered in 25 to 30%. In view of the fact that more recently, in outbreaks of primary atypical pneumonia in Army camps, unilateral involvement of the lungs has been noted frequently,[8] the

differentiation by Roentgen ray between primary atypical pneumonia and pneumococcic pneumonia is made extremely difficult.

TABLE 1.—ROENTGEN RAY FINDINGS IN ADULT PNEUMONIA IN HARLEM HOSPITAL JULY 1, 1939 TO MARCH 1, 1943

Pneumococcus types	Roentgen Ray Findings: Bilateral (%)	Roentgen Ray Findings: Unilateral (%)	Total No. of cases	Type incidence in % of total
I	10.5	89.5	239	17.1
II	8.0	92.0	100	7.2
III	14.0	86.0	272	19.5
VII	5.7	94.3	279	20.0
VIII	4.8	95.2	189	13.5
XII	0.0	100.0	32	2.3
XIII	9.1	90.9	22	1.6
XIV	8.5	91.5	71	5.1
XV	21.4	78.6	14	1.0
XIX	5.3	94.7	75	5.3
XXV	10.7	89.3	56	4.0
XXXIII	10.4	89.6	48	3.4
Grand totals	8.8	91.2	1397	100.0

TABLE 2.—RESPONSE TO SULFONAMIDE THERAPY IN ADULT PNEUMONIA PATIENTS IN HARLEM HOSPITAL, JULY 1, 1939 TO MARCH 1, 1943

Pneumococcus types	Roentgen ray findings: Bilateral: Total No. of cases*	Bilateral: Response in less than 48 hours (%)	Bilateral: No response in 48 hours (%)	Unilateral: Total No. of cases*	Unilateral: Response in less than 48 hours (%)	Unilateral: No response in 48 hours (%)
I	10	50.0	50.0	125	63.2	36.8
II	4	25.0	75.0	46	69.7	30.3
III	21	28.5	71.5	143	60.1	39.9
VII	12	33.3	66.7	156	59.6	40.4
VIII	6	66.7	33.3	117	56.5	43.5
XII	0	0	0	22	40.9	59.1
XIII	2	50.0	50.0	18	66.7	33.3
XIV	4	25.0	75.0	41	48.8	51.2
XV	1	0	100.0	9	44.5	55.5
XIX	3	33.3	66.7	60	31.6	68.4
XXV	3	33.3	66.7	34	52.9	47.1
XXXIII	4	50.0	50.0	30	66.6	33.4
No pathogens	14	35.7	64.3	77	31.1	68.9
Total	84	36.8	63.2	878	53.3	46.7

* Deaths in less than 48 hours omitted.

Comment on Table 2. Response to chemotherapy has been designated as a fall in temperature within 48 hours, with subsequent recovery. The choice of 48 hours is purely arbitrary. A fall in temperature by lysis may also be due to chemotherapy, but this is difficult of interpretation. Therefore, this table does not necessarily represent the true and complete effectiveness of sulfonamide therapy.

Of patients with pneumonia due to the common as well as the higher types (except XII and XIX), with unilateral involvement, about 60% responded to chemotherapy within 48 hours. In the cases where no pathogens were found in the sputum, 30% responded in 48 hours. In the group with bilateral involvement the results are less favorable

for all types. Only about 35% of this group responded in 48 hours. The same incidence of response was found in the group where no pathogens were found in sputum. These figures indicate that a response to chemotherapy is not necessarily an important diagnostic aid in the differential diagnosis between pneumococcic pneumonia and primary atypical pneumonia.

Discussion. From the cases and tables presented above, it can be seen that not infrequently the pneumococcic pneumonias show features characteristic of primary atypical pneumonia. Among these are bilateral patchy infiltration (Table 1); failure to respond to chemotherapy (Table 2); presence of cold agglutinins (Cases 4 and 5); relative bradycardia (Cases 1, 2 and 3); spiking temperature (Case 3); normal leukocyte count or leukopenia (Cases 1 and 4); dry cough with scanty sputum; frontal headache, and so on.

Many investigators reporting cases of primary atypical pneumonia have found higher types of pneumococci in the sputum of their patients. Some have regarded these higher types as possible secondary invaders to a primary viral infection, but they have been disregarded by most investigators. The occurrence of positive blood cultures reported in pneumonia caused by the higher types (10 to 15%), the appearance of agglutinins in rising titer, the isolation of organisms from chest fluids, lung suctions and autopsies, and the response to serum therapy,[3] however, stamp these higher types as active invaders.

Recently, Thomas *et al.*[11] have isolated an indifferent streptococcus from the lungs of a fatal case of primary atypical pneumonia. The convalescent serum obtained from 55 of their 101 cases of atypical pneumonia gave positive agglutination reactions with this streptococcus. These authors have also obtained similar strains of indifferent streptococcus from other fatal cases. The rôle of this organism as possible primary or secondary invader has not been established as yet. In cases where no pathogens are found in the sputum, the possibility of a bacterial invader cannot be ruled out on this observation alone. It is generally accepted that in tuberculosis the finding of acid-fast organisms in sputum is dependent on the type of lesion and on a free communication between the lesion and a bronchus. Negative sputum findings in miliary tuberculosis of the lung is common experience. A similar mechanism may play a rôle in the failure to isolate pneumococci from cases of pneumococcic pneumonia.* Recently 8 out of 20 cases of this group were "typed" for pneumococci by the "reverse" typing method.[10]

There are cases which resemble the primary atypical pneumonias clinically and respond well to chemotherapy. Worthy of note is the "no pathogens in sputum" group in which 33% of the cases responded within 48 hours. On the other hand, 40% of the pneumococcic pneumonias failed to respond within 48 hours. Many cases of Types XII, XIX and III may be cited as examples (Table 2). On several occasions,

* From the data of lung suctions done previously at Harlem Hospital, it was found that in about 6% of the cases the etiologic organism was found in the lesion and not in the sputum.

however, infections caused by these types have responded well to serum therapy.*

It is difficult to estimate the incidence of atypical forms in patients with pneumococcic pneumonia. If one accepts as the main criteria of atypical pneumonia a patchy, bronchopneumonic infiltration of the lungs and failure to respond to chemotherapy, then the incidence of atypical cases of pneumococcic pneumonia is about 20%.

It appears, therefore, that a differentiation between primary atypical pneumonia and pneumococcic pneumonia on the basis of clinical findings alone, is difficult. It is recommended that every effort be made in cases of primary atypical pneumonia, particularly where its occurrence is sporadic, to rule out the pneumococcus as a possible etiologic agent or as secondary invader, before denying the patient sulfonamide or serum therapy.

It is hoped that the wider use of penicillin for the treatment of pneumonic cases will afford an additional useful criterion for the differentiation of pneumococcic pneumonia and primary atypical pneumonia.

Summary. 1. The similarity between sporadic cases of primary atypical pneumonia and pneumococcic pneumonia has been illustrated by presentation of 5 representative case reports as well as data obtained from the study of large series of cases.

2. The Roentgen ray findings and lack of response to chemotherapy were not found to be of significant value in the diagnosis of sporadic cases of primary atypical pneumonia.

3. "Reverse" typing as an aid in diagnosis of pneumococcic pneumonia is suggested.

4. Of patients with pneumonia from whom no pathogenic bacteria were isolated from sputum, 33% responded to sulfonamide therapy within 48 hours.

5. Clinically, differentiation between atypical pneumococcic pneumonia and primary atypical pneumonia may be difficult. A bacteriologic etiology should be carefully ruled out before denying the patient chemotherapy or specific serum treatment.

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* From a table published by Finland,[3] a similar conclusion can be drawn. For example, 27.7% of his Type XII pneumococcus cases which received no treatment, 12.7% which received chemotherapy, and only 2.5% which received serum, died. This holds also to a lesser extent, for Types XX, XXV and XXVII pneumococcic pneumonia.

ROENTGEN THERAPY OF BOECK'S SARCOID

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Pathology and Diagnosis. The cause of sarcoid and its relationship to tuberculosis are matters that remain in dispute. Schaumann, who is given credit for establishing the relationship of many of the clinical entities that now are recognized as a feature of this disease, regarded it as an atypical form of tuberculosis, but others have taken issue with this view.[2] Recent studies indicate that the lesions of sarcoid may involve practically every organ or system in the body, but show a predilection for the lymph nodes and other structures of the reticulo-endothelial system.[11] Regardless of location the histologic appearance of the process is strikingly uniform and, as Pinner[9] remarks, "There is not only uniformity but monotony in regard to these lesions." The basic lesion is the epithelioid cell tubercle with occasional giant cells of the Langhans type and with an absence of caseation, and only occasionally some central necrosis. Because of the microscopic appearance, pathologists are prone to classify the disease as hyperplastic or non-caseous tuberculosis.[10]

Probably the most frequent sites of involvement, clinically, are the mediastinal lymph nodes and the pulmonary tissues, which makes the disease of particular interest to roentgenologists. We agree with Longcope[6] that it no longer can be regarded as a rarity. Since the lesions of sarcoid can occur in the lungs and mediastinum without cutaneous or other external manifestations, and since the pulmonary lesions, even though extensive, may exist without clinical signs, Roentgen examination of the chest plays an important rôle in its detection. Enlargement of the mediastinal lymph nodes is an almost invariable feature. The enlarged nodes produce soft, lobulated shadows in the hila or along the upper mediastinum, occasionally forming broad masses overlying the base of the heart and the great vessels. The outer borders are not as sharply delineated as is commonly seen in Hodgkin's disease and other forms of lymphoblastoma, but the extent of involvement may be almost as great. Such lymph node enlargement may occur with or without associated pulmonary lesions. When the lungs are involved, the lesions vary greatly in appearance. Usually widely distributed, they may appear as coarse, patchy densities; irregular striations; fibrous strands; or even as a uniformly disseminated, finely nodular or miliary process. The wide dissemination, the multiplicity of types of pulmonary shadows present and the concomitant mediastinal lymph

node enlargement are features which should lead one to suspect sarcoid.[5] When correlated with the clinical aspects and other laboratory data the diagnosis becomes more certain. The mildness of clinical symptoms often is entirely out of proportion to the extent of the disease as seen roentgenologically, and extensive lesions at times may be found more or less accidentally in the chest when there is little in the clinical picture to suggest their presence. Because of the usually benign nature of the process and the tendency for spontaneous recovery over periods of time, frequently a matter of several years, it may never be possible to obtain tissues for microscopic study and the diagnosis often must remain presumptive.

Treatment. Treatment has usually been purely empirical and includes the use of arsenicals, tuberculin, leprosol, iodides, gold salts, hyperpyrexia, ultra-violet irradiation, Roentgen rays and radium. The latter have been successful in the treatment of skin lesions, particularly the Darier-Roussy type, and also in the Boeck lesion.[7] Evaluation of any form of treatment is difficult because of the tendency of the lesions to spontaneous resolution.

Earlier workers have not found Roentgen ray therapy of benefit in the systemic lesions. Middleton[8] sums up this experience in the latest edition of Cecil's "Textbook of Medicine" with the statement that Roentgen ray and radium therapy offer nothing in this disease. Recently, however, several reports on the treatment of enlarged lymph nodes and of hilar and pulmonary sarcoid have been favorable. Harrell[3] treated 1 case, but at the time of the report the period of observation had been too short for evaluation; Bernstein and Oppenheimer[1] used Roentgen ray therapy in 4 of their 6 cases with very encouraging results; however, they believe that radiosensitivity may depend upon the stage of the disease at the time when treatment is instituted; and Katz *et al.*[4] report 1 case in which there was definite reduction in the size of hilar nodes following Roentgen irradiation. In the yearbooks of Radiology, no mention has been made of the use of Roentgen rays in the treatment of sarcoidosis, except for an editorial note suggesting a therapeutic trial because of the similarity of some of the cases to Hodgkin's disease.[12] British workers[13] report the treatment of hyperplastic tuberculosis by Roentgen therapy with good results, but the differential diagnosis is made between Boeck's sarcoid and hyperplastic tuberculosis. The terms are not used synonymously as they are in much of the American literature; consequently, it is impossible to determine whether or not some of the cases reviewed could be considered in the sarcoid group by the diagnostic criteria used in this country.

In order to obtain a more definite and current opinion regarding this problem, we sent questionnaires to 33 radiologists in this country and in Canada, chosen so as to give a fairly complete geographic representation. Four questions were asked: Have you treated patients with Boeck's sarcoid of the lung with Roentgen rays? If so, how many? What technique did you use? What were the results? Is there any other comment you care to make? Thirty-one replies were received

and the results are compiled in Table 1; the information given there speaks for itself. It seems apparent that very few cases of Boeck's sarcoid have been treated by Roentgen rays; the majority of those approached have had no experience with it and some advise against it.

In the past 2 years 14 patients have been treated by Roentgen rays for the chest lesions of Boeck's sarcoid in the Department of Radiology at the State of Wisconsin General Hospital; 8 of these have been observed sufficiently long to warrant certain preliminary conclusions. Within the period of observation, 6 of the 8 have shown definite roentgenologic evidence of improvement. In 2 cases the patients had been followed for periods of 22 and 23 months, respectively, before therapy was started, and the course in each case had been constantly progressive. It is of interest to note that clinical improvement preceded objective evidence in most cases, and that in the 6 cases in which roentgenograms demonstrated regression of the lesion, the objective improvement was manifested in from 2 to 4 months after therapy was started. Of the remaining 2 cases of the series, 1 showed improvement in 5 months after treatment, and the other patient failed to return for follow-up studies or treatment at regular intervals.

TABLE 1.—QUESTIONNAIRE ON ROENTGEN-RAY TREATMENT OF BOECK'S SARCOID

No.	No. of patients treated	Technique	Results	Comment
21	None			
1	..	....	....	Too few to express opinion
1	1	Not given	....	1 case with cervical nodes; favorable
1	1	Not given	Too early	Advise Roentgen ray therapy
1	1	75–150 r; 2× p.w., then 1/mo.	Very good	
1	2	2400–4800 r, 4 fields; HVL_{Cu} = 1 mm.	Recovery	Treats to differentiate between sarcoid and Hodgkins
1	3	100–200 r; 4–5 × 2 fields; HVL_{Cu} = 1.1 mm.	2 improved; 1 no follow-up	1 case also cervical nodes involved
1	3	100 r, 1 field daily; 500 r total per field; HVL_{Cu} = 1 mm.	1 improved, 2 not	Do not advise Roentgen ray therapy
1	4	HVL_{Cu} = 1.3 mm.; dose not given	Good	2 proved by biopsy; 2 had generalized involvement with visual disturbance; normal vision restored in 1
1	6	750–900 r divided in 3–4 doses A and P; HVL_{Cu} = 1 mm.	No benefit in most; 1 worse	Advise against Roentgen ray therapy
1	6	1200 r to each area; HVL_{Cu} = 1 mm.	No improvement	

The method of treatment has been 6 exposures of 150 r (in air) to the anterior and posterior mediastinum (15 x 20 cm. port), one area daily, using 175 kv., half-value layer = 1.05 mm. Cu. Patients returned in 6 weeks to 2 months and received a second series, using the same factors, except for 1 patient whose lesions had cleared almost completely in the interval. Two patients received a third series after a

second 2-month interval. Other glands involved usually receive 3 x 150 r (in air), daily or every other day, which may be repeated once or twice at intervals of 4 to 6 weeks.

Case Reports. CASE 1 (No. 11238). R. H., a 28 year old white male, was first seen at the State of Wisconsin General Hospital April 10, 1942, with the history of cough productive of ½ cup of mucopurulent, blood-flecked sputum for 6 months and of chest pain for a month. He complained also of dyspnea, wheezing, and hoarseness. His appetite was good, and he had had no weight loss. The symptoms were accompanied by a low grade fever up to 100° F. Physical examination was negative except for shotty cervical adenopathy and decreased resonance, increased vocal and tactile fremitus and decreased expansion of the right hemithorax. There were coarse rhonchi over the entire chest, but most pronounced at the right base. Laboratory findings were hemoglobin 14.8, R.B.C. 4,460,000, W.B.C. 6000 (neutrophils 65%, lymphocytes 31%, monocytes 2%, and eosinophils 2%); negative urinalysis; and a sedimentation rate of 27 mm. in 60 minutes. The tuberculin reaction was negative, and gastric aspirations for tubercle bacilli were negative by smear and by guinea pig inoculation. A roentgenogram of the chest showed soft thickening of the hilum shadows bilaterally, more pronounced on the right with associated soft infiltrative extension out into the mid- and basal lung fields (Fig. 1*a*). Roentgenograms of the bones of the hands were negative.

The diagnosis of Boeck's sarcoid was made and the patient was given Roentgen ray therapy to the mediastinum. When he returned for check-up examination after 3 months on July 17, 1942, he had resumed work; he had no dyspnea and very little cough; the chest roentgenogram showed marked improvement with clearing of the hilar thickening and of the soft opacity below the right hilum (Fig. 1*b*). He was last seen January 21, 1943, at which time he felt well and his chest had returned to normal.

CASE 2 (No. 11555). W. G., a 29 year old white male, was admitted July 20, 1942, with a history of non-tender swelling of the parotid glands bilaterally of 1 month's duration and associated with a low grade fever. He had had no dryness of the mouth nor noted other swollen glands. The systemic history was negative; he had had mumps as a child; there was no history of tuberculosis. Physical examination was negative except for firm, non-tender swelling of the parotid glands bilaterally; the liver was palpable just below the costal margin. Laboratory studies included a negative urinalysis; hemoglobin 16.6 gm., R.B.C. 5,370,000, W.B.C. 6950 (neutrophils 66%; lymphocytes 26%; monocytes 2%; and eosinophils 4%). A roentgenogram of the chest showed moderate, but definite enlargement of the hilum lymph nodes, more pronounced on the right side (Fig. 2*a*). A tentative diagnosis of Boeck's sarcoid was made.

The patient returned August 5, 1942 for biopsy and at that time the tuberculin test with 0.01 mg. and 0.1 mg. and the coccidioidin test were negative, as were gastric aspirations for tubercle bacilli. The total serum protein was 5.3 gm. with 3.5 gm. albumin, 1.8 gm. globulin and an A/G ratio of 1.9. A roentgenogram of the chest showed slight increase in hilum adenopathy. The biopsy of the parotid was diagnosed Boeck's sarcoid (Fig. 3*a*). Roentgen therapy was started to the mediastinum on August 8, and he received 6 treatments. He returned October 9 and was given a second series of 4 treatments. The parotid swelling had decreased, but there was no change in the roentgenogram of the chest. He received his third series starting January 18, 1943, at which time the roentgenograms showed almost complete regression of the hilum adenopathy. Following therapy, he developed some stringy density in the right upper lobe, but roentgenograms on November 29, 1943, showed regression of these lesions, and the patient continued to be symptom-free and afebrile (Fig. 2*b*).

CASE 3 (No. 11680). M. Jo., a 53 year old white woman, was first admitted to the State of Wisconsin General Hospital on July 13, 1942, with a severe menopausal syndrome and an associated vomiting and weight loss. Marked

hilar thickenings were noted on roentgenoscopic examination of the gastrointestinal tract, and subsequent roentgenograms of the chest showed marked

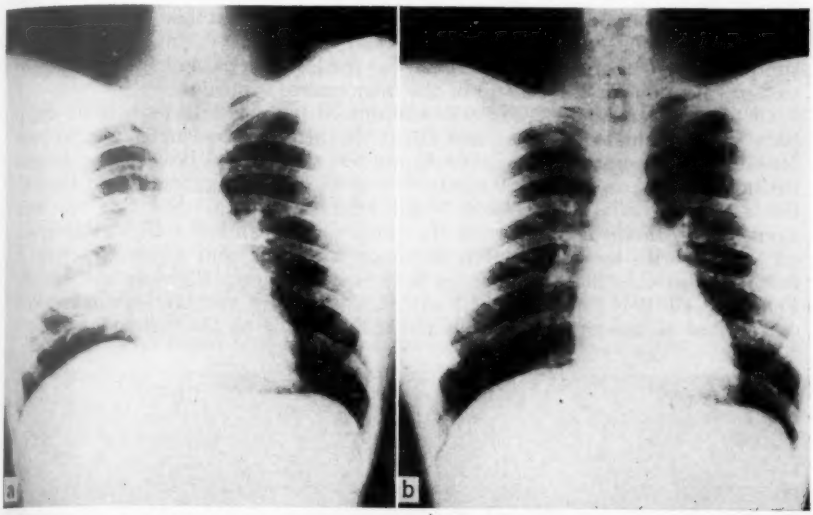

FIG. 1.—*a*, Soft thickening of the hilum shadows bilaterally, more pronounced on the right with soft infiltrative extension out into the mid- and basal lung fields (April 15, 1942). *b*, Clearing of the hilar thickening and of the soft opacity below the right hilum (July 17, 1942).

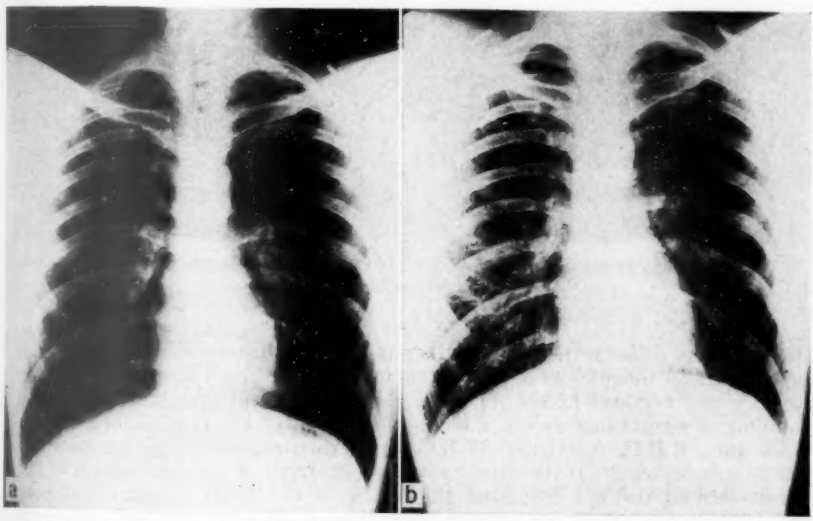

FIG. 2.—*a*, Moderate but definite enlargement of the hilum lymph nodes, more pronounced on the right side (July 22, 1942). *b*, Definite regression of lesions shown in *a* (November 29, 1943).

nodular thickening of both hilum shadows with associated coarse striated densities extending out into the mid-zone of the left lung field and toward the base on the right. She had no other adenopathy and neither chest findings

on physical examination nor symptoms referable to the chest. The urinalysis was negative; hemoglobin 13.3 gm., R.B.C. 4,300,000, W.B.C. 9000 (neutrophils 54%; lymphocytes 38%; monocytes 8%); gastric aspirations were negative for tubercle bacilli by smear and by culture; total serum proteins, 5.4 gm. with 2.1 gm. albumin, 3.3 gm. globulin and an A/G ratio of 0.6. The tuberculin test with 0.01 mg. and 0.1 mg., and coccidioidin tests were negative. A presumptive diagnosis of Boeck's sarcoid was made. The patient was discharged with medication for the control of the menopausal syndrome.

On September 20, 1942, she was readmitted because of intermittent sharp pain in the right lower chest and slight dyspnea and continued weight loss. Roentgen ray therapy to the mediastinum was started, but because the patient became nauseated only 5 treatments were given. A roentgenogram on December 2 showed definite regression of the hilar thickening. She was not seen again until March 3, 1943, when the chest showed almost complete clearing on the left with moderate enlargement on the right, and a second series of Roentgen ray treatments was given to the mediastinum. She was last seen on February 17, 1944, when she felt well, and the chest roentgenogram showed no residual on the left and only minimal thickening on the right.

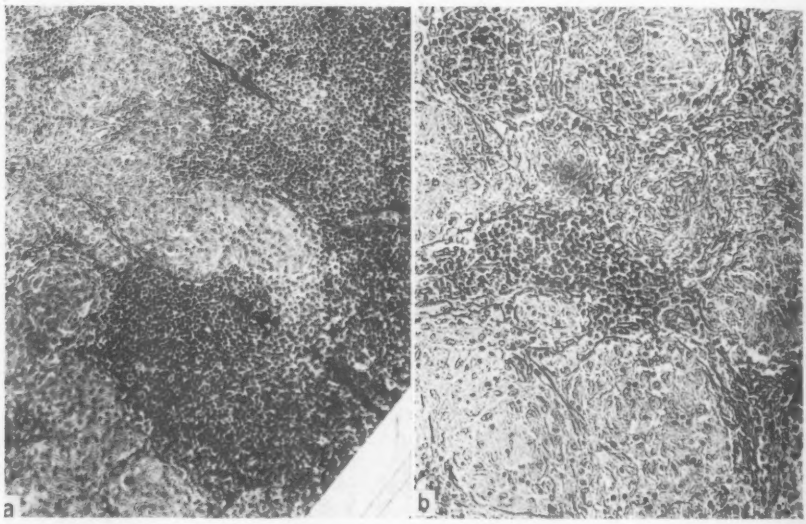

FIG. 3.—*a*, Photomicrogram of biopsy of the parotid gland in Case 2. *b*, Photomicrogram of biopsy of left axillary node of Case 6.

CASE 4 (No. 11761). I. Q., a 56 year old white woman, was admitted to the State of Wisconsin General Hospital with a history of nausea, loss of appetite, and weight loss of 20 pounds in the preceding 4 months. Systemic history was negative except for a dry cough. Physical examination revealed nothing of significance except a temperature of 101° F. The hemoglobin was 16.6 gm., R.B.C. 5,200,000, W.B.C. 4650 (neutrophils 59%; lymphocytes 39%; monocytes 2%); the urinalysis was negative. A roentgenogram of the chest showed distinct lobulated thickening of the hilum shadows on both sides and widening of the supracardiac shadow to the right and anteriorly due to involvement of the paratracheal lymph nodes. The pulmonary parenchyma was clear. A diagnosis of Boeck's sarcoid was made. She was readmitted on October 12, 1942; the roentgenogram of the chest showed no change and Roentgen therapy to the mediastinum was started. A second and third series were given in December, 1942, and in February, 1943. Roentgenograms showed slight, but definite regression on December 19, 1942, and return to normal on October 2, 1943.

CASE 5 (No. 12208). M. Ja., a 61 year old white female, was admitted to the State of Wisconsin General Hospital on March 23, 1943, with attacks of redness of the right eye with blurring of vision over a period of 3 years. In January, 1943, she had a more severe attack associated with pain; the family physician found the tension increased and started the administration of pilocarpine. The systemic history was not significant. Physical examination was negative except for the eyes. The urinalysis was negative; hemoglobin 16.9 gm., R.B.C. 5,260,000, W.B.C. 4350 (neutrophils 45%; lymphocytes 49%; monocytes 2%; eosinophils 4%); the total serum protein was 6.9 gm. with 3.4 gm. albumin, 3.5 gm. globulin and an A/G ratio of 0.97. A chest roentgenogram revealed scattered nodular infiltrations in the lung fields with an associated mild tracheobronchial lymphadenopathy. A diagnosis of sarcoidosis with chest involvement, uveitis and secondary glaucoma was made; local treatment was administered to control the glaucoma and Roentgen ray therapy to the mediastinum was started. The patient returned May 26, 1943, for follow-up examination. The glaucoma had been well controlled, but the chest lesions had advanced moderately. A second series of Roentgen ray therapy was given to the mediastinum. The patient failed to return until January 26, 1944. She had discontinued the use of the prescribed eye drops and reëntered the hospital because of a recurrence of symptoms of glaucoma. A roentgenogram of the chest showed minimal regression of the nodular lesions. The tuberculin tests, both 0.01 mg. and 0.1 mg. were negative. The patient refused to remain for further Roentgen ray therapy.

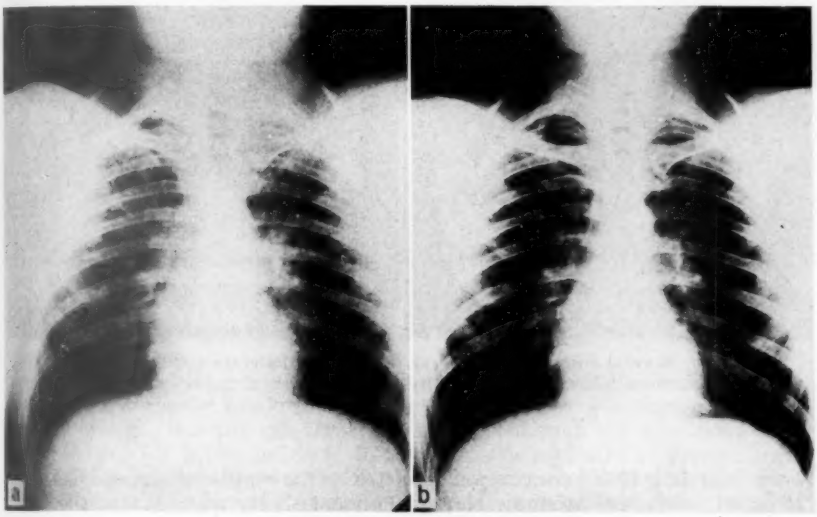

FIG. 4.—*a*, Numerous coarse nodular shadows in the parenchyma, more numerous in the upper two-thirds and associated with fibrous strands extending out from the soft, well-defined, enlarged hilar nodes bilaterally (June 6, 1941). *b*, Definite regression of lesions shown in *a* (March 16, 1944).

CASE 6 (No. 10444). H. D., a 34 year old white male, was first admitted to the State of Wisconsin General Hospital on June 15, 1941, with the history of swelling of the cervical, axillary and inguinal glands since 1938, and of increasing dyspnea and dysphagia. In February, 1941 he had had a tonsillectomy, because of frequent colds and sore throats; healing was delayed. At that time, a node from the left axilla had been biopsied and was reported hyperplastic tuberculosis (Fig. 3*b*). The patient was sent to a sanatorium where he was always afebrile and repeated tuberculin tests and gastric aspirations for tubercle bacilli were negative. On physical examination at the time

of admission, a small ulcerated lesion was noted in the left nostril; this had been present for 2 or 3 years. There was also a generalized adenopathy, and a palpable liver and spleen. The chest was negative. The hemoglobin was 15.2 gm., R.B.C. were 5,370,000, W.B.C. 7350 (neutrophils 79%; lymphocytes 11%; monocytes 8%; eosinophils 2%); gastric aspirations for acid-fast organisms and tuberculin tests remained negative and the sedimentation rate was 21 mm. in 60 minutes. The roentgenogram of the chest showed numerous coarse, nodular shadows in the parenchyma, more numerous in the upper two-thirds and associated with fibrous strands extending out from soft, well-defined enlarged hilum nodes bilaterally (Fig. 4*a*). At that time, Roentgen ray therapy was given to the cervical nodes, 3 x 150 r (in air), 175 kv., half value layer = 1.05 mm. Cu, 10 x 10 cm.^{2} field, and he was returned to the sanatorium.

The patient was seen at intervals for the next 2 years and received further therapy to various enlarged glands with good results. Although the chest lesions progressed as shown in the roentgenograms, gastric tests remained negative and the patient was discharged from the sanatorium.

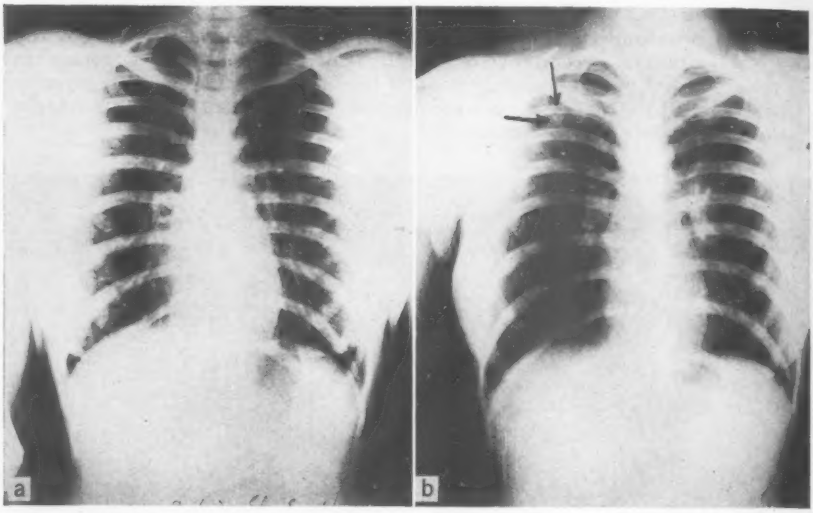

FIG. 5.—*a*, Normal chest (November 11, 1940). *b*, Moderate nodular thickening of the hilum shadows bilaterally; general soft accentuation of trunk markings in both lungs with a small area of nodular infiltration in the right apex (see arrows) (June 23, 1941).

On March 2, 1943 he was again admitted to the State of Wisconsin General Hospital for further studies. He had minimal shotty adenopathy, the previously mentioned lesion in the left nostril, and in addition a 3 cm. red, non-tender nodule in the right axilla and bilateral dacrocystitis. The blood count and urinalysis were normal; the total serum protein was 7.5 gm. with 3.2 gm. albumin, 4.3 gm. globulin, and an A/G ratio of 0.7; coccidioidin skin tests were negative. Roentgenograms of the bones of the hands and feet showed no cystic lesions. Roentgen ray therapy to the mediastinum was then given. On June 22, 1943 a roentgenogram of the chest showed some increase in the lesions, but the patient was unable to remain for treatment. However, when he returned for the second series August 23, early signs of resolution were apparent, and he was working for the first time in more than 2 years. When last seen on March 16, 1944, the chest lesions had undergone uniform regression in size, and there was no significant adenopathy (Fig. 4*b*).

CASE 7 (No. 12342). E. D., a 22 year old white woman, was first seen for routine examination at the time of employment by the State of Wisconsin

General Hospital on August 31, 1939, when physical examination and chest roentgenogram were essentially negative. A routine chest roentgenogram on November 11, 1940 (Fig. 5*a*) was also negative. On June 23, 1941 she asked for an examination because of substernal pain of 1 week's duration and throat clearing for the preceding 2 or 3 months. Her weight had been at the lower limits of her normal variation for several months. Chest roentgenograms demonstrated distinct, but moderate nodular thickening of the hilum shadows bilaterally and rather general soft accentuation of trunk markings in both lungs, together with a small area of nodular infiltration in the right apex (Fig. 5*b*). W.B.C. numbered 6050 (neutrophils 50%; lymphocytes 47%; monocytes 2%; eosinophils 1%); gastric aspirations for acid-fast organisms by smear and by guinea pig inoculation were negative.

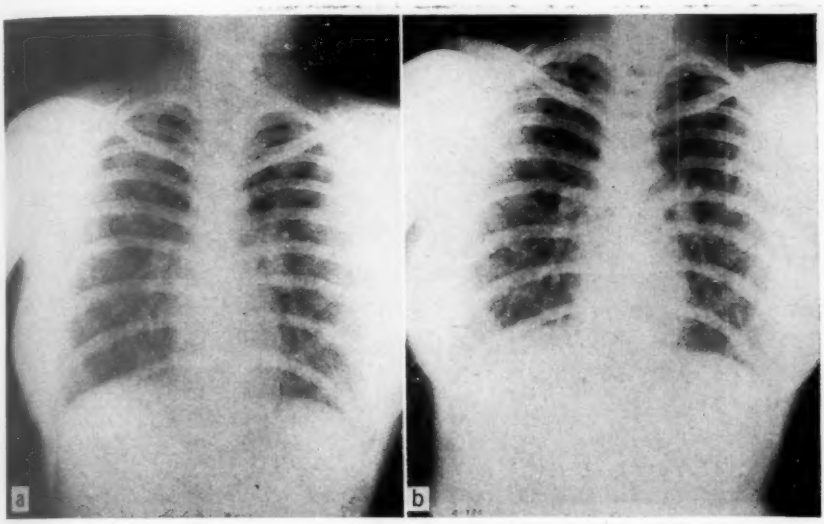

FIG. 6.—*a*, Further increase in the pulmonary lesions shown in Figure 5*b* (November 19, 1942). *b*, Bilateral hilar thickening and fine granular nodularity with some stringy density throughout the lung fields (June 2, 1943).

During the following 2 years the patient was kept at strictly limited activity and followed closely. She was afebrile, had no cough or expectoration, had gained weight, but the substernal pain persisted and she developed mild arthralgia of her hands and feet. Repeated gastric aspirations remained negative for tubercle bacilli except on one occasion when one organism was found in the smear, but the culture from the same specimen was negative. The tuberculin test with 0.01 mg. was negative; 0.1 mg. gave a 2 x 2 cm.^{2} reaction. About 1 year after the onset, her menses became irregular and a mass 4 to 5 cm. in diameter was found on the right side of the pelvis. There was a gradual increase in the pulmonary lesions (Fig. 6*a*) until a chest roentgenogram in June, 1943 showed bilateral hilar thickening and fine granular nodularity with some stringy density throughout the lung fields (Fig. 6*b*), and a presumptive diagnosis of sarcoidosis was made. Roentgen ray therapy to the mediastinum was started June 3, 1943. On August 2, 1943 a roentgenogram of the chest showed slight, but definite regression of the lesions, and a second series of treatments was given. The roentgenogram taken on October 4, 1943 (Fig. 7*a*) demonstrated almost complete clearing of the process, and in follow-up studies on March 6, 1944 and June 5, 1944 (Fig. 7*b*) there was no evidence of recurrence.

CASE 8 (No. 12712). D. F., a 48-year old Jewish woman was admitted to the State of Wisconsin General Hospital on October 19, 1943 with the history

of hard, painful nodules on her legs for the preceding 9 months; vague joint pains particularly in her wrists and fingers for 6 or 7 months; episodes of cramping abdominal pain and fever for 3 months; and a feeling of oppression in her chest of 3 to 4 months' duration. On physical examination the nodules were observed to be discrete, firm, immovable, red or bluish red, and varying in size from 1 to 4 cm. There was no adenopathy; the liver was palpable 3 cm. below the costal margin; the spleen was not palpable. There were a few moist râles at both lung bases and there was a soft systolic murmur at the cardiac apex transmitted to the left axilla. The urinalysis was negative; the hemoglobin was 14.3 gm., R.B.C. were 5,000,000, W.B.C. 6800 (neutrophils 71%; lymphocytes 20%; monocytes 4%; eosinophils 5%); sedimentation rate 4 mm.

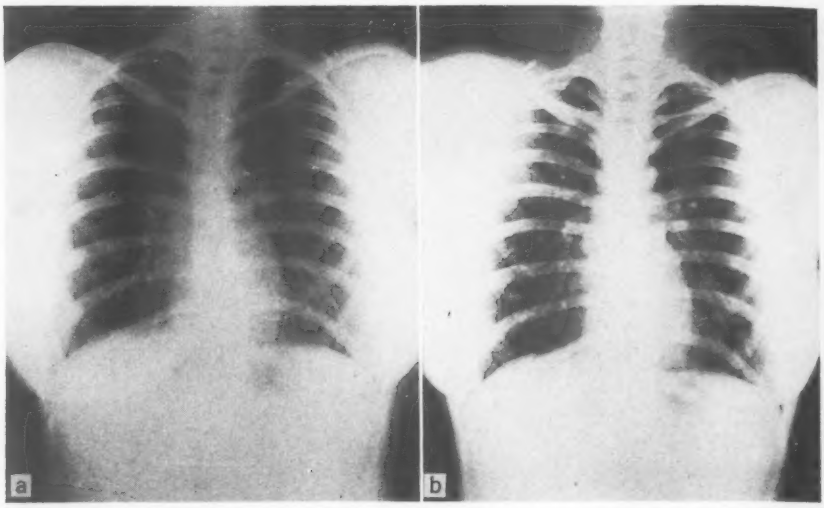

FIG. 7.—*a*, Almost complete clearing of the process shown in Figure 6*b* (October 4, 1943). *b*, No evidence of recurrence approximately 1 year after the treatment (June 5, 1944).

in 60 minutes; the ECG was normal. Roentgenographic findings were lobular thickening of the hilum shadows on both sides of fairly soft character with mild accentuation of trunk shadows in the lower lobes bilaterally. A diagnosis of erythema nodosum and Boeck's sarcoid was made and Roentgen ray therapy to the mediastinum given. The patient returned December 27, 1943 for a second series of treatments. The chest remained unchanged, but the patient had improved clinically. Likewise no change was demonstrated when the patient was seen in February, 1944, but on the examination May 24, 1944, definite regression was found.

Comment. The relatively small number of cases does not permit a statistical evaluation of the age and sex distribution beyond the statement that the majority of the patients were females and belonged to the middle-aged group. No definite relationship between type and severity of involvement, duration of the disease and response to treatment can so far be established. In 2 instances the diagnosis was proved by biopsy; in the remaining patients it rested on Roentgen examination only. In 4 of the first 8 cases the therapeutic result was good, in 1 instance excellent, in 1 satisfactory and in 2 only fair. The

patient described in Case 7 is perhaps the most interesting and convincing one because of the long duration and progressive character of the pathologic process as proved roentgenologically—2 years before Roentgen ray therapy—and because of the striking response to treatment. No untoward reactions were observed in any one of the treated cases, and therefore we would like to encourage other radiologists to give Roentgen ray therapy in Boeck's sarcoid a trial. More observations and further studies are, of course, necessary before a final verdict as to the efficacy of the treatment proposed can definitely be determined.

Summary. 1. The pathologic aspect and the Roentgen diagnosis of Boeck's sarcoid are briefly discussed.

2. Our experience with Roentgen rays in the treatment of this disease, based on the study of 14 patients, 8 of which were observed sufficiently long to draw preliminary conclusions, is related.

3. Since the results were favorable in the majority of cases and no untoward effects observed, the use of Roentgen rays in the treatment of Boeck's sarcoid is recommended in order to arrive at a definite opinion regarding its true efficacy.

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THE TREATMENT OF TULAREMIA WITH INTRAVENOUS BISMUTH SODIUM TARTRATE

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Tularemia is showing an increasing incidence. It is possible that it is being recognized more frequently. It would seem constructive and timely, therefore, to present a new and effective form of treatment. With the exception of a few general comments concerning

incidence, morbidity and mortality, this report will be limited to its diagnosis and clinical management.

In reviewing the literature it becomes apparent that considerable confusion exists regarding the methods of transmission of tularemia and its various types, their morbidity and mortality.

Pasteurella tularensis (*Bacterium tularense*). In 1912, it had been found in more than 20 forms of wild life (McCoy and Chapin) and since then many others have been added. The current list includes rabbits, hares, squirrels, prairie dogs and a variety of small fur-bearing animals, both wild and domestic—sheep, dogs, cats, rats and mice; numerous fowls—quails, sage hens and chickens; and various arthropods such as flies, fleas, bed-bugs, ticks and lice.

The last-named group is usually responsible for animal-to-animal transmission, while man may become inoculated by handling the fur or tissues of the infected animal, by eating its meat, by inhalation of dust containing the organism, by handling the pasteurella in the bacteriologic laboratory, or by a direct bite of one of these insects, particularly the ticks (wood tick—*Dermacentor andersoni*, and dog tick—*Dermacentor variabilis*). Here in Arkansas at least 90% of our cases result from tick bites, and it is disturbing to note that in ticks, hereditary transmission has been demonstrated through eggs, larvæ and nymphs.[1]

Tularemia is a relatively recent disease. The causative organism was first isolated from ground squirrels in 1911 by McCoy and Chapin[2] in Tulare County, California, while first clinical recognition was by Wherry and Lamb in 1914.[3] Cecil[4] now records over 10,118 known cases in 46 states and the District of Columbia. He further points out that although tularemia occurs in every month of the year, it is most prevalent in tick regions in March to August, deerfly areas June to September, due to jack rabbits in April to October, and cottontail rabbits in November and June. Foreign distribution includes Canada, Scandinavia, northern and eastern Europe, Russia, Turkey and Japan.

The usually described forms of tularemia are those most frequently encountered. They include (1) the ulceroglandular type, which exhibits an ulcerating papular lesion at the site of inoculation, with definite regional lymphadenitis, with or without suppuration; (2) the glandular type, presenting the lymphadenitis without the primary lesion; (3) the oculoglandular type, with initial infection of the conjunctiva and secondary participation of neighboring lymphatics; (4) the oral, or anginal form, usually acquired by eating inadequately cooked infected meats, and characterized by an acute, painful, ulcerative pharyngitis or nasopharyngitis, enlargement of the submaxillary and cervical lymph nodes, and gastro-intestinal manifestations; and (5) the "typhoid," or cryptogenic type, which presents a toxemia with a prolonged and debilitating pyrexia, but without the primary lesion or lymphadenitis. This latter type is seen most frequently in laboratory workers.

Pleuropulmonary manifestations[5] are often recorded, including atypical pneumonia, lung abscess, acute or chronic bronchitis and

pleurisy with effusion, accompanied by mediastinal and peribronchial lymphadenitis. Meningeal or leptomeningeal involvement, usually fatal, has been reported with recovery of *B. tularense* from the spinal fluid, and diffuse encephalitis in acute tularemia has been demonstrated at autopsy by Hartman. Foshay[6,7] has discussed coronary occlusions and angina pectoris as tularemic complications, Saphir[8] has dealt with myocarditis, while Aagaard[9] recently reviewed the pericardial involvements, reporting 2 adult cases.

In some quarters tularemia appears to be regarded as a trivial affair, tending to spontaneous recovery with a minor degree of morbidity and a mortality rate of less than 5%. This would seem to apply only to a select group of the mild uncomplicated infections. Cecil[4] quotes Foshay, "The mean duration of fever is 26 days, the duration of the adenopathy from 3 to 4 months, and the duration of the disease 5½ months." He points out that pulmonary tularemia has a "high rate of fatality (62.5%)." Averaging all types, Foshay cites a mortality of 6%; Simpson 11%; Jager and Ransmeier[10] review 9 cases of constrictive pericarditis with 33% mortality, while Stitt, Clough and Clough[1] mention 12 fatalities of 20 cases resulting from the ingestion of insufficiently cooked rabbit meat.

From the Shreveport Louisiana Charity Hospital, W. R. Mathews[11] reports similarly acquired infections with 4 deaths in a family of 5, exhibiting acute pharyngeal lesions suggestive of diphtheria. He states the tularemic mortality in that hospital to be "approximately 11% for white patients and 32% for colored."[12]

In this region tularemia is frequently encountered. In the past 3 years I have seen or been consulted about 61 cases. All have been treated by the intravenous injection of a water-soluble bismuth, with prompt recovery, while within the limited investigations we have been able to conduct, we have learned of no case of tularemia with positive blood cultures, other than the ones treated with intravenous bismuth, which have lived for more than 14 days.

The geographic distribution of these 61 cases was Arkansas, Oklahoma, Missouri, Kansas, Louisiana and Texas. All but 3 were within the area bounded by the water sheds of the Red River on the south and the White River on the north.

In 57 cases the source of infection was a tick bite; 1 was a squirrel bite; 3 were hand infections, acquired by skinning rabbits. Since the tick plays the dominant rôle as the source of infection in this region, most of the patients have been loggers or farmers working in wooded tracts with brush undergrowth.

Six cases were Negroes, 55 were whites. All Negro cases were of the mild "typhoid" type, none presenting acute throat symptoms. This limited number did not permit confirmation of the observation by Mathews that in the Red River section the Negro death rate is 3 times that of the white man.

Every tularemic tick bite on the lower extremity developed a bubo on the corresponding side. In no case was this bilateral. Two cases presented lesions on the penis, one an ulcer on the dorsal corona, the other an ulcer on the anterior surface at the base of the shaft. One of these developed a right-sided bubo, the other a left.

Twenty-one cases with lesions on the arms or upper torso all showed an axillary adenitis, but in only 2 did the glands progress to suppuration. No reason is apparent as to why the inguinal glands break down and the axillary do not. Epitrochlear glands suppurated in 2 cases, the same forearm in each case presenting the initial lesion.

In this series, the incubation period has been within relatively fixed limits. The initial chill and malaise occurred between 72 and 120 hours after discovery of the tick and its removal from the skin.

Agglutination tests were routinely done on all cases when first seen. All but 2 showed positive titers of 1:360 or over. Of these 2 the titers reached 1:360 in 1 on the 17th day and in the other on the 18th day. The treatment employed did not interfere with the agglutination titer.

Blood cultures were made on 50 cases of the lymphoglandular type, with only 16 proven positive. The mild typhoid type cases were not cultured.

The inoculation of laboratory animals with the patient's blood, or material obtained from the glands or other lesions, was not employed, due to the inherent delay of the procedure in serving as an aid in diagnosis.

Treatment. We are familiar with the purely symptomatic treatment of these cases and have tried the various therapeutic agents suggested from time to time, without impressive results. Our experience with the Foshay Specific Antiserum has been disappointing, and more recently a trial of several of the sulfonamide compounds resulted in no clinical improvement whatever. Two of my associates, who have had an opportunity to conduct significant trials of penicillin in combating this gram-negative bacillus, report it to be ineffective. With none of these methods has symptomatic relief been striking or the return to usual activities as prompt as with the use of intravenous bismuth.

Bismuth Treatment. Intravenous injections of the bismuth solution were started in all of these cases at the time of their first visit, without awaiting laboratory findings. In most instances this was on the 3rd or 4th day after the patient was aware of being sick. Early diagnosis and treatment is imperative with other than the mild typhoid type of tularemia. If treatment is postponed, particularly in those cases presenting positive blood cultures, the death rate will be extremely high. Even in persons gravely ill, because of the delay in completing titrations, and in view of the high percentage of negative cultures from initial lesions, glands or blood in the early stages of the infection, the diagnosis must be made and treatment started without the aid of the laboratory. Usually the characteristic clinical onset and the history of exposure to probable infection will supply the necessary evidence.

Originally we employed other aqueous bismuth preparations, but during the last 2 years we have used a solution of bismuth sodium tartrate, prepared especially for experimental intravenous use.* It

* Supplied by G. D. Searle & Co. A 2% bismuth sodium tartrate solution containing 29.6 mg. of bismuth per cc., and buffered with sucrose to isotonicity.

appears more effective than any of the bismuth salts previously employed, possibly due to the chemical nature of the bismuth complex.

The solution does not irritate the vein intima, and in our experience any local inflammation has been due to the inadvertent injection of it outside the vein. We routinely employ a 25 to 26 gauge needle to avoid injury to the vein walls.

Untoward effects have been practically *nil*. Reactions of nausea and vomiting are seen occasionally, but much less frequently than with any of the arsenicals. In the few persons who developed nausea immediately after the injection, a level teaspoonful of sodium bicarbonate in water, orally, minimizes this gastric symptom. In no case has it been necessary to stop the injections.

No circulatory evidence of shock has ever been seen. Although diarrhea has occurred rarely in the course of treatment of other conditions by intravenous bismuth, it has been encountered in none of these tularemics.

Gingivitis has not occurred in any case in this series. It is far less common than with the intramuscular use of bismuth, and only 2 cases of gingivitis have been observed in 7 years' experience with intravenous bismuth administration.

The dose is estimated on the basis of 1 cc. to 100 pounds of body weight. In children under the age of 15 the dose may be relatively larger, estimated at approximately 1 cc. for 40 to 50 pounds of weight. For an adult the initial injection is 1 to 1.25 cc. to test the tolerance of the patient. Through a small needle the speed of injection is of no importance. If nausea does not follow the first injection, the dose is increased according to the weight scale, at the next injection. This dose is administered intravenously each day until the temperature reaches a daily maximum of 99°. The injections are then given on alternate days for 4 treatments, then twice a week for 4 more weeks.

In our scheme of treatment the necrotic glands are not incised. Instead, the skin is infiltrated with novocain, a sharp No. 18 needle is plunged into the gland and the contents aspirated with a Luer syringe. By this release of pressure from the overlying skin, necrosis is prevented and suppuration with drainage avoided.

The average number of bismuth injections required to secure the clinical picture of recovery has been 7; the smallest number was 4; the longest series of daily injections necessary to establish a normal temperature, with clinical evidence of recovery, was 18.

In this series of 61 cases of tularemia treated with intravenous bismuth sodium tartrate, no death has occurred. It has proved, in this area, a specific procedure in the treatment of this disease.

Bismuth Intravenously. In view of the widely prevalent belief that bismuth should never be administered intravenously, a comment or two on this misconception may be in order.

In the past 7 years 90,000 intravenous injections of bismuth have been given to nearly 700 patients. The diseases have included lues, bronchial spirillum infections, bronchiectasis, pulmonary tuberculosis, acute tonsillitis, actinomycosis and tularemia. In no instance

has there been a reaction to compare in severity with that which frequently accompanies the intravenous use of the arsenicals.

Children tolerate intravenous bismuth especially well. Numerous youngsters from 4 to 7 years have received from 0.75 to 1 cc. of the currently employed solution, twice weekly for 6 months or more without untoward effects of any type. In these ages the tolerance of a 40 pound child appears to be approximately 1 cc. These prolonged series of injections were in the treatment of pathologies other than tularemia, and are mentioned here only in refutation of the commonly accepted dictum that intravenous bismuth is highly toxic to the human. The statement has been made by numerous pediatricians that *children* do not stand bismuth well, referring to its intramuscular injection. By intravenous administration we have not found this true.

There is the hypothesis that intravenous bismuth might prove effective against some of the rickettsias; we have typhus particularly in mind. Typhus does not appear in this section in sufficient numbers to provide an opinion, but it is hoped that bismuth sodium tartrate will be tried intravenously by clinicians having such cases available.

The toxicity of the older monotartrate of bismuth is not characteristic of the more recent aqueous soluble forms, when employed intravenously in the human. As compared with the intramuscular administration the intravenous routing provides definite differences in clinical action, all advantageous. The dictum that bismuth is a one-way drug, *i. e.*, intramuscular, is nonetheless false because it has been, and is being today, solemnly intoned.

Sufficient for the clinician is the knowledge that a drug is safe and non-toxic within reasonable limits, and that it carries the potential of benefit or cure for a disease entity. Bismuth sodium tartrate intravenously, so serves against tularemia.

Case Reports. CASE 1. B. J., male Negro, age 7, weight 42 pounds.

His dog caught a rabbit Sept. 5, 1943, and he and his 2 companions skinned it. It was not eaten by any members of the family, contrary to usual rule.

The ulcer developed at the base of the nail, second digit, right hand, where previously he had had a scratch. His chill, temperature and malaise developed 94 hours after skinning the rabbit. Neither of the other 2 boys became ill.

He was first seen 6 days after the contact. His temperature was 102°, a lymphadenitis was present in both epitrochlear and axillary regions, most marked on right. The blood titer was 3+ in 1:360 dilution.

Intravenous injections of bismuth sodium tartrate, 1 cc. daily, were started on the day first seen. Since children under 12 years of age tolerate intravenous bismuth in twice the weight-scale of adults, this boy with a weight of 42 pounds, showed no evidence of excessive dosage.

The axillary glands did not break down, conforming to our routine experience. He received 4 daily intravenous injections, all during office visits. He was not restricted to bed at any time. The temperature remained below 99° after the fourth injection. He then received 8 more injections, 2 per week, with complete recovery.

CASE 2. R. L. W., male, white, age 17, weight 125 pounds.

Always a resident of New York City, he came to visit a farm near Hot Springs, Ark., May 2, 1943. While roaming about the woods the first day, he received multiple tick bites on both legs and thighs. One small ulcer developed on the right anterior tibial region, the site from which a tick had been removed 84 hours prior to the initial chill and malaise.

Bismuth sodium tartrate was given intravenously when first seen, after taking a blood specimen for agglutination tests. The titer was 4+ in 1:360 dilution on the first test. The bismuth solution dosage was 1 cc. to 100 pounds of weight.

He received 5 daily injections, followed by 2 per week for 3 weeks. The temperature remained below 99° after the fifth daily injection. All injections were given at the office.

A bubo developed in the right inguinal chain, conforming to the observation that in these cases the inguinal glands will break down on one side only, while the axillaries will enlarge but not suppurate.

This patient lost no weight, was not confined to bed at any time, and returned to New York within a month of his infection, fully recovered.

CASE 3. J. W. L., male, white, age 55, weight 175 pounds.

On the evening of May 22, 1943, after a day of cutting brush on his farm, two ticks were removed from the right upper arm at the insertion of the deltoid muscle. The initial chill, followed by temperature and malaise, occurred 80 hours after the ticks were discovered.

The attending doctors suspected tularemia but remained uncertain for 18 days, during which time they submitted daily blood specimens to the laboratory in an effort to obtain a positive agglutination titer. The titer on the 18th day was a 4+ in a 1:360 dilution. During this 18-day period he had received sulfathiazole and aspirin, with no effect upon his temperature, which had a daily range to 104° and 105°. He had lost 32 pounds of weight.

Intravenous bismuth sodium tartrate was started the 18th day, and given daily in a dosage based on 1 cc. to 100 pounds of weight.

At the time of the seventh daily injection the temperature remained below 99.6° the entire day. Injections were then given on alternate days for 12 days, during which the temperature remained below this level. He then received 2 injections per week for 6 weeks. He was able to come to the office for treatments 15 days after the first injection, and thereafter progressed to uneventful recovery.

This case illustrates the hazard of awaiting laboratory confirmation of tularemia, since the positive titer may be delayed, and such delays in treatment make serious inroads on the resistance of the patient. Tularemia can always be diagnosed clinically; the laboratory findings are only confirmatory.

Conclusion. Sixty-one consecutive cases of tularemia are reported, including various types, all treated, with prompt recovery, by intravenous injections of a solution of bismuth sodium tartrate, especially prepared for intravenous application.

The use of this solution has proved a specific procedure in the treatment of tularemia.

Contrary to prevalent views, the intravenously administered bismuth is quite free from serious untoward manifestations. This opinion is based upon some 90,000 intravenous injections in approximately 700 cases, extending over a period of 7 years, and including a variety of pathologic conditions.

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VITAMIN CONTENT OF LIVER EXTRACTS FOR PARENTERAL USE

A Comparison of Crude and Concentrated Preparations

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In this brief paper we shall attempt to answer the frequent requests for quantitative data on the vitamin B factors present in liver extract for parenteral use. The quantitative variations in the several factors present in different brands of liver extract are in part due to the distinct processes employed. Since we are dealing with preformed substances stored in liver, the amount of which is dependent in part upon the nutrition of the animal, it is obvious that even when employing the same extraction process there may be some variations in yields. It is hoped that a comparison of the data on the concentrated extracts with those on the crude extracts will be of help in evaluating these dilute, unrefined preparations.

Material and Methods. The liver extracts, conforming to U.S.P. standards, included in this report represent random samples of leading brands obtained through a wholesale druggist and, through our Control Laboratory, unselected samples of our own manufacture. These extracts have been assayed by the microbiologic methods now in general use for riboflavin,[3] niacin,[4] pantothenic acid[5] and *L. casei* factor (B_C)[2]. Total solids and total nitrogen values are also included. For various reasons it has not been possible to determine pyridoxine (B_6) or choline. Since the thiamine content of parenteral liver is negligible, this factor is omitted from the study. The data presented in Table 1 reflect in a relative manner the effects of the various processing procedures.

In recent years numerous references to the use of "crude" liver extract have appeared in the medical literature. The confusion caused by the loose use of this term should come to an end now that the First Supplement of U.S.P. XII (p. 36) contains a definition of "Liver Injection (Crude)." Although each manufacturer of liver extract prepares material corresponding to Cohn's G fraction, there are many modifications of the original procedure which, in turn, result in marked differences in color, in the content of total solids, total nitrogen, the anti-anemic substance and the several components of the B complex. One of the steps in general use calls for the addition to a syrupy concentrate of the original water extract of sufficient 95% alcohol to obtain

a mixture containing 65% alcohol by volume. The anti-anemic substance, plus varying amounts of the B complex factors stay in solution in the water-alcohol mixture, leaving a voluminous tarlike residue which contains by far the major portion of the B complex factors (extracted by water in the first stage). This step is essential, as it is the principal means by which proteins and other inert substances are removed from the original extract; and so it makes possible the preparation of injectable solutions. The processing steps from this point on are quite different and each manufacturer is careful to protect his methods of purification and concentration. Apparently those who favor the parenteral use of the crude liver extracts are not employing such material in the treatment of pernicious anemia, but use the crude preparations for non-specific therapy principally because of the belief that larger amounts of the several B complex factors are present in these crude extracts.

Results. The results of the analytical work (calculated per cc. and per U.S.P. XII unit injectable) are presented in Table 1. As the standard for comparison in our study of liver extracts we have prepared the crude, unfractionated extract obtained as the first step in the manufacture of all liver preparations, No. 21*e* in Table 1. It is important to an understanding of this discussion to keep in mind that this crude extract contains the maximum amount of each of the several B factors extractable from whole liver by an acid-water infusion, pH 5±. Using this material as a "yard stick" and taking extract No. 1 in Table 1 as an example, we have in this refined and concentrated extract only 1.5 μg. of riboflavin as compared with 1914 μg. in the crude standard. In other words, only 0.08% of the riboflavin content of the crude extract remains in the highly concentrated material. Using the same unfractionated extract as the standard, an examination of the data for each of the 6 highly refined and concentrated preparations (containing 15 units injectable per cc.), Nos. 1 to 6 in Table 1, shows that the content of:

Riboflavin	varies	from	0.08	to	10.7%	of	quantity	present	in	the standard
Niacin	"	"	1.4	"	40.0%	"	"	"	"	"
Pantothenic acid	"	"	0.6	"	32.0%	"	"	"	"	"
L. casei factor (B_c)	"	"	0.08	"	1.0%	"	"	"	"	"

Similarly, a study of the data for each of the 3 crude extracts, Nos. 11, 12, 13*c*, Table 1 (2 units injectable per cc.), shows that the content of:

Riboflavin	varies	from	0.07	to	4.8%	of	quantity	present	in	the standard
Niacin	"	"	4.00	"	16.0%	"	"	"	"	"
Pantothenic acid	"	"	3.60	"	18.0%	"	"	"	"	"
L. casei factor (B_c)	"	"	0.09	"	7.0%	"	"	"	"	"

Those who favor the parenteral use of the crude liver extracts are not primarily interested in the treatment of pernicious anemia; hence there would appear to be no reason to make comparisons based on the values obtained when the several B factors are shown in relation to

TABLE 1.—ANALYTICAL DATA ON LIVER EXTRACTS

Sample	U.S.P. units per cc.	Total solids Milligrams		Total nitrogen Milligrams		Riboflavin Micrograms*		Niacin Micrograms*		Pantothenic acid Micrograms*		*L. casei* factor (B_c) Micrograms*	
		Per cc.	Per unit	Per cc.	Per unit	Per cc.	Per unit	Per cc.	Per unit	Per cc.	Per unit	Per cc.	Per unit
						Parenteral Liver Extracts							
1	15	73	5	8	0.5	1.5	0.1	2290	153	1210	81	0.73	0.05
2	15	216	14	22	1.4	99.6	6.6	205	14	185	12	5.56	0.37
3	15	194	13	28	1.9	205.0	13.7	109	7	31	2	8.72	0.58
4	15	235	16	33	2.2	136.5	9.1	1270	85	155	10	2.66	0.18
5*a*	15	79	5	13	0.9	2.1	0.1	204	14	5	0.4	0.88	0.06
6*b*	15	215	14	27	1.8	1.9	0.1	3160	211	1710	114	0.75	0.05
7	10	103	10	13	1.3	1.0	0.1	1316	132	816	82	0.40	0.04
8	10	99	10	10	1.0	9.3	0.9	1600	160	940	94	0.20	0.02
9	4	329	82	23	6.8	51.6	12.9	1430	358	379	95	2.22	0.55
10	3.3	178	54	14	4.3	1.2	0.4	270	81	191	58	2.63	0.80
11	2	295	148	35	17.5	92.7	46.4	305	153	191	95	4.06	2.03
12	2	290	145	20	10.0	76.0	38.0	1220	610	330	165	0.76	0.38
13*c*	2	349	175	31	15.3	2.2	1.1	954	477	569	285	1.01	0.50
14	1	256	256	16	16.0	26.4	26.4	672	672	272	272	3.67	3.67
15	1	143	143	9	9.0	31.3	31.3	614	614	98	98	0.20	0.20
16*d*	1	177	177	16	16.0	1.2	1.2	492	492	306	306	1.09	1.09
						Oral Liver Extracts							
17	60 cc.–I.U.	143	8,580	9	540.0	0.5	31.7	349	20,940	150	9,012	0.21	12.30
18	45 cc.–I.U.	121	5,445	9	423.0	34.1	1,534.5	327	14,670	88	3,960	2.60	117.00
19	45 cc.–I.U.	517	23,260	38	1724.0	232.0	10,422.0	1010	45,450	235	10,575	1.69	76.00
20	12.75 gm.–I.U.	..	..	91*k*	1160.0*k*	254.0*k*	3,237.2*k*	792*k*	10,096*k*	449*k*	5,725*k*	5.92*k*	75.50*k*
21*e*	Unfractionated Conc.	..	..	59*m*	..	1914.0*m*	..	7783*m*	..	5280*m*	..	57.60*m*	

* 1 mg. = 1000 μg. (or gammas).

a Not a domestic product but appears in the list of U.S.P. products.

b Made by an approved process; standardization in progress.

c Made by an approved process; standardization in progress.

d A dilution of *c* with equal volume of normal saline solution.

e A concentrate of the total extractives obtained by an acceptable process from pork liver.

k Results expressed in micrograms per gram of powdered extract.

m Results expressed in micrograms per 100 gm. of liver used.

each unit of the anti-anemic substance. In all probability these crude preparations will be given frequently in doses of 1 to 5 cc. for non-specific liver therapy. It might be well at this point to set forth, as far as the available data will permit, just what would be included in a 5 cc. injection of highly concentrated material (15 units per cc.) as contrasted with 5 cc. of crude extract containing 2 units per cc. In making this comparison we have averaged the values for four concentrated preparations containing 15 units per cc. (Nos. 1, 2, 3 and 4, Table 1) and three crude liver extracts containing 2 units per cc. (Nos. 11, 12, 13*c*, Table 1). The results are as follows:

	Micrograms per 5 cc.			
	Riboflavin	Niacin	Pantothenic acid	*L. casei* factor
Concentrated	553	4842	1975	22.1
Crude	285	4130	1816	9.7

From these figures it is evident that 5 cc. of the concentrated extract provide, in addition to 75 units of anti-anemic material, 1.9 times as much riboflavin, 1.1 times as much niacin, 1.1 times as much pantothenic acid, and 2.2 times as much *L. casei* factor, as would be obtained by the use of 5 cc. of crude extract.

The data for 3 liquid oral extracts (Nos. 17, 18, 19, Table 1) and one powder (No. 20, Table 1) for peroral use indicate the same variations in the content of the several B factors as are shown by the products for parenteral use. In general, the preparations for oral use do not compare favorably (as to B factor content) with either the crude or refined preparations for parenteral use. The average values for the 4 oral preparations are:

Micrograms per 5 cc. (Nos. 17, 18, 19, Table 1) or 5 gm. (No. 20, Table 1)			
Riboflavin	Niacin	Pantothenic acid	*L. casei* factor
650	3098	1153	13.05

Discussion. There is no evidence to date to indicate that any one of the well-recognized B factors is directly involved in hematopoiesis in pernicious anemia.[1] Sufficient time has now elapsed to establish by clinical experience that refined, concentrated liver extracts are highly effective in the control of the signs and symptoms associated with pernicious anemia. The data reported in this paper show that the crude extracts contain on the average less riboflavin, niacin, pantothenic acid and *L. casei* factor (B_c) than do the refined, concentrated preparations. There thus appears to be little justification for the preferred use of crude liver extracts in the treatment of Addisonian pernicious anemia or as a source of the several B factors included in this report. It is possible that continued work in this field will reveal the presence of other nutritional factors which may have a quite different distribution.

Summary. A quantitative study of U.S.P. crude and refined liver extracts indicates that, on the average, the refined preparations contain

c Made by an approved process; standardization in progress.
d A dilution of *c* with equal volume of normal saline solution.
e A concentrate of the total extractives obtained by an acceptable process from pork liver.
k Results expressed in micrograms per gram of powdered extract.
m Results expressed in micrograms per 100 gm. of liver used.

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as much or more riboflavin, niacin, pantothenic acid and *L. casei* (B_c) than do the crude preparations.

The writer is appreciative of the assistance rendered by our Analytical and Control Departments for the data presented in Table 1.

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PROGRESS
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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF
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BIOLOGIC FALSE POSITIVE REACTIONS TO THE TESTS FOR SYPHILIS

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THE Wassermann and flocculation procedures were originally regarded as specific reactions. Soon after their introduction, however, falsely positive reactions were repeatedly reported with practically all tests, not only in many non-syphilitic diseases of human beings, but in presumably normal non-syphilitic individuals as well. At first these non-specific reactions were thought to be due largely to technical errors, except in the case of leprosy and malaria. In 1926, Stokes[289a] reëmphasized the very proper distinction which should be drawn in all discussion of the Wassermann test between false positive results which are due to detectable errors in technique and non-specific positives due to biologic and unavoidable sources of error. He stated that no procedure had as yet been brought to light which could do away with the consequences of technical mishandling and incorrect carrying out of instructions. He predicted, however, that biologic non-specific positives could conceivably, by perfection of procedure with an increase in the specificity of the test, be entirely done away with *if instructions were exactly followed.* In 1929, under the title of "The Problem of Pseudo-Syphilis," Stokes[289b] made an extended report of the problem of non-specific positive reactions based on personal experience with individual cases and on the knowledge of the times. Blumenthal and Mallinckrodt-Haupt[22] in Jadassohn's Handbuch in 1929 presented an elaborate discussion of this problem.

Since then much attention has been paid to this subject, and it has resulted in attempts at standardization of serologic procedure through a group of serologic surveys conducted by the United States Public Health Service in coöperation with the American Society of Clinical Pathologists, in a group of important studies from the Johns Hopkins Hospital Syphilis Clinic under the directionof Dr. J. E. Moore[2,11] in the appearance of special tests and procedures to "verify" positive serologic reactions, by the revival of the use of certain "specific" antigens (spirochetal), the recommendation of certain clinical and laboratory schemes for the establishment

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of the verity or falseness of a serologic reaction to the tests for syphilis, and in the appearance of a number of comprehensive reviews of the entire subject of the problem of falsely positive reactions in the serologic tests for syphilis.[57,128,161b,165i,206,211,248,290]

The importance of this problem is further emphasized by the fact that serologic tests for syphilis are being used more and more widely on civilian and military personnel. Because of non-specific positive reactions, many individuals have been stigmatized as syphilitic and have been given unnecessary treatment on the basis of reactions disclosed by routine serologic examinations in the course of or immediately following a non-syphilitic disease. The use of serodiagnostic tests for compulsory pre-induction, prenatal, premarital, preëmployment, and other routine purposes makes the problem of false positive serologic reactions for syphilis of paramount importance.

Classification and Criteria of Diagnosis of False Positive Reactions. The simplest classification of the positive serologic reactions obtained in non-syphilitic individuals is that of Stokes,[289b] in which false positives due to biologic and unavoidable sources of error are differentiated from false positives due to technical errors. The terminology in this field, according to Sulzberger[294] tends toward confusion. He claims that such terms as "false positive" or "biologic reaction" are inexact and carry erroneous implications. A positive result which is repeatable and not due to a technical error should not be called false; and the positive reaction with a syphilitic serum is a biologic positive, just as positive as a positive result with a serum of a malarial or leprous patient. He proposes the following "non-prejudicial" terms and definitions: (1) *positive syphilitic reaction* for the positive results with serums from proved syphilitics; (2) *positive non-syphilitic reaction* for the positive results with serums from patients proved to be non-syphilitic, in those instances in which the reactions cannot be attributed to technical errors; (3) *positive malarial* (or postvaccination, etc.) *reaction*, specifying the conditions to which the positive result can be proved to have been due, and (4) *false positive* when the reaction can be shown to be due to technical or other errors.

The incidence of false positive reactions will vary depending on the criteria used for the determination of a case as being false. Many reports deal with only transient positive reactions as false positive. These erroneously and automatically call syphilitic any case in which the positive reactions persist for more than a few months. It is conceivable that a patient with syphilis may also be subject to biologic false reactions. This may be the basis for some of the so-called fixed positives (seroresistance). Some indicate that a false positive reaction is one in which only one type of test gives the positive result. Repetition of tests is a *sine qua non* of diagnosis of false positive reaction. Use of social criteria leads to a situation facetiously stated by Stokes[289a] in 1926 as follows: (There are) "instances in which one Wassermann test will convict a laborer over his own denial, two will make a case against a banker or a railroad president, but three successive positives will scarcely convince the medical adviser of the 'guilt' of a clergyman."

Until recently there has been no real universally accepted standard for approval of serologic performance, the result being that the same specimen submitted to one laboratory, even tested with the supposedly same serologic procedure, would give grossly different results. It seems that even when performed by the originators of the tests under seemingly ideal conditions but at different times and in different places, the most dependable

and widely accepted serologic tests do not give uniform results, either as to specificity or as to sensitivity. Stokes, Beerman and Ingraham[290] in their review of the problem, stated that substantial agreement has been reached as the result of international and national conferences on the following points:

1. Absolute uniformity among test results on a single specimen cannot be expected.

2. Precipitation tests should be supplemented by complement fixation procedure either performed routinely or available if the result of the precipitation test is doubtful.

3. In this country at least, only five procedures are sufficiently well performed by a sufficient number of laboratories to deserve the title of "approved." These are the Kolmer Wassermann test; the Eagle, Kahn, Hinton and Kline precipitation procedures. While there is no bar advisable to the performance of other types of tests, they should be regarded in the effort to provide a dependable national serologic service, as research procedures rather than practice procedures. If additional tests are performed by any laboratory they should be a matter for supplementary report and should not be admitted to the status of "approved" until their repeated evaluation in national serologic conferences establishes their distinctive superiority.

4. The specificity of serologic tests is in general more important than their sensitivity. Specificity should be practically 100%, and in laboratory grouping and approval status, a specificity rating below 99% on 200 test specimens or 98% on 100 specimens should lead to the temporary exclusion of the test from the approved list until such time as modification reëstablishes a rating for it of 100%. Sensitivity on the other hand—"an approved sensitivity rating shall not be more than 20% below that of the control laboratory in cases of late or treated syphilis and within 1% of that of the control laboratory in cases of untreated and secondary syphilis."

Unfortunately, the reported cases involving so-called false positive reactions in the literature have not been examined by such strict criteria as standardized serologic procedure would demand.

The question of sensitivity *versus* specificity of a serologic procedure must be considered in evaluating the serologic findings in a given case. Every increase in sensitiveness of a test for syphilis, that is in its ability to identify the disease in the absence of clinical signs, must be measured against the risk of pinning a partial or completely false finding upon a person who does not have the disease. It is more important, however, for practical purposes, that high specificity rather than sensitivity be accepted as the primary recommendation of a serologic procedure. Kahn[146e] has clearly pointed out if the ratio of syphilitic cases to non-syphilitic cases in the population is kept minimal, how much more misleading is a small error in specificity as compared with a large error in sensitivity. For example, he showed in a hypothetical case, that in 40,000 hospital admissions, with 1200 cases of treated and untreated syphilis among them, an increase of 1% in sensitivity means 12 cases of treated or untreated syphilis reported positive, while 1% increase in non-specificity means 400 non-syphilitic persons reported positive.

Another criterion which is too frequently invoked in estimating whether a serologic reaction is true or false is the strength of the reaction. False reactions are usually considered to be of low titer. For example, even Eagle[71g] says: "Unlike the case of animal sera, many of which give frankly positive and even high-titered diagnostic tests for syphilis in the absence

of that disease, the reactivity of normal human sera with flocculation antigens is usually only minimal in degree, requires refined techniques for its demonstration and is usually not apparent in the diagnostic tests. It is possible that the occasional human serum which gives false positive diagnostic tests contains an excess of this normal factor ordinarily present only in traces. It is equally possible that such biologic false reactions bear no relationship to the normal flocculating activity of human serum and are due to an entirely different substance."

This supposedly usually low titer of biologic false positive reactions is even considered "fortunate" by Weil.[316] This view leads the uncritical to conclude that one may easily differentiate a true from a false reaction merely on the basis of titer. There is no doubt that the quantitative procedure has failed as a significant differential procedure between true and biologic false reactions, but this should not be construed as a condemnation of this procedure in a scheme designed to differentiate false from true positive.

The reactions in another group of diseases must be considered, which, for practical purposes, may be called "syphilis-like" or, as Rein and Elsberg[248] call them, "syphiloid" diseases. These include the treponematoses such as yaws, bejel, and the disease lately admitted to this group, pinta. Strictly speaking, the reactions obtained in these diseases are true rather than false positives.

Recent compilations of the causes of false positive reactions are given by Stokes, Beerman and Ingraham,[290] by Rein and Elsberg[248] by Kolmer[165i] and by Eagle.[71e]

While it is not our intention to discuss in detail technical false positive reactions, a certain amount of attention must be given to the nature of the antigen. The most troublesome and perhaps the most frequent cause of false positive reactions in tests for syphilis is rated by Kline as the presence in the antigen emulsions themselves of adventitious materials. A full discussion of the subject of the antigen, including cardiolipin, is discussed in numerous studies.[57,115,116,161a,230,290,316]

Another confusing item which must be taken into account in dealing with serologic results is the question of zone reactions. This is the phenomenon in serologic reactions in which one observes that stronger concentrations of serum may give negative results or weaker concentrations of the serum may give strongly positive reactions. This subject has been well summarized by Eagle,[71e] Greene and Breazele,[102] Myers and Perry,[218] Owen, Brooks and Tucker,[228] and Kolmer and Lynch.[170]

Syphilologists are familiar with the "false negative" reactions which occur in seronegative primary syphilis, late syphilis of the heart, and neuroaxis and in treatment-resistant syphilis (Beerman[14a]). The whole subject of false negative reactions is reviewed by Hinrichsen,[128] Rein and Frank,[249] and by Souders.[282]

Factors Involved in the Incidence of False Positive Serologic Reactions of Syphilis. Rein and Elsberg[248] have well summarized a number of factors which are concerned in the investigation of false positive serologic reactions, each of which will affect the incidence of such reactions.

1. Serologic Reactors. These are individuals who are more likely to develop false positive blood reactions for syphilis than others. For example, Rein and Elsberg[248] found that in their investigation of the smallpox vaccination group some individuals with insignificant vaccinoid reactions developed false positive serologic reactions while other individuals with the most severe vaccinia reactions remained seronegative throughout their

study. Similar observations were made in other diseases. Rein and Elsberg[248] were unable to determine whether these false reactions were due to:

(*a*) The development of antibodies similar to syphilitic reagin.
(*b*) An increase in the seroglobulins.
(*c*) An altered or labile globulin fraction.
(*d*) Any other change in the immunochemical mechanism.

2. Type of the Non-syphilitic Disease. Certain diseases appear to be more likely to produce false positive serologic reactions than others. Leprosy and malaria seem to be among the worst offenders. Individuals with upper respiratory infections only occasionally develop false positive reactions while tuberculosis rarely produces such phenomena.

3. Incubation Period for the Development of False Positive Serologic Reactions. Rein and Elsberg[248] indicate that a definite period of time must elapse following the onset of most diseases before the false positive reactions are first detected. This period varies with different diseases and conditions. The optimal time for the detection of most false positive reactions seems to be between the 7th and 21st day of the disease.

4. Number of Tests Employed in the Serologic Battery. The number of detectable false positive reactions will increase in proportion to the number of tests employed in the serologic battery. At the Army Medical School, Rein uses a battery of 6 tests for all serologic consultations and serologic investigations. (Kline Diagnostic, Kline Exclusion, Boerner-Jones-Lukens, Mazzini, Kahn Standard and Kolmer.) The use of this battery of tests has yielded Rein and Elsberg[248] a higher incidence of false positive reactions than that obtained by others in similar studies.

5. Types of Tests. The results of the serologic survey conducted by the United States Public Health Service in collaboration with the American Society of Clinical Pathologists have shown in the case of author serologist performance that certain tests give more false positive reactions than others. The incidence of false positive reactions was not necessarily directly proportional to the sensitivity of the tests, that certain diseases give fewer false positive reactions with one test than with another, and that certain tests give fewer false positive reactions with one disease and more with another disease. Rein and Elsberg[248] have indicated from preliminary studies that there is evidence to show that the "*serologic patterns*" of false positive reactions may vary from one disease to another according to the type of tests used. For example, individuals with primary atypical pneumonia, upper respiratory infection and smallpox vaccinations rarely develop false positive serologic reactions with a Kolmer complement fixation test, whereas the incidence is quite high with the 5 flocculation tests. There is some feeling that on the whole, because of lack of controls, the flocculation procedures are apt to yield more false positive reactions than the complement fixation tests.

6. Intervals of Testing. The incidence of false positive reactions may be increased by performing the serologic examinations at more frequent intervals. Sometimes it is necessary to do daily serologic examinations to catch the positive reactions of low titer which may tend to revert to negativity within a few days. Such transient reactions would be missed if the intervals of testing were too long.

7. Duration of False Positives. From the studies of Rein and Elsberg[248] at the Army Medical School, it would appear that in most instances the maximum titer of false positive reactions was obtained be-

tween the 10th and 14th day following the onset of a febrile disease or following vaccination. The length of time an individual continued to show false positive reactions appeared to depend on the degree of positivity reached on the 10th to the 14th day. The majority of serums with false positive reactions developing as a result of a limited febrile disease or smallpox vaccination became negative within 3 or 4 months. Rein and Elsberg[248] state that some individuals may continue to get false positive reactions for several years for no apparent reason.

Familial Tendency to Biologic False Positive Reactions. This has been noted rarely in some recent reports. Lindau[182] reported a family in which the parents and their 2 children were all serologically positive for syphilis for 1 month following an attack of bronchitis. W. Smith[277] encountered positive reactions in 2 young siblings 6 weeks after mumps. Zuger and Moffat[328] recorded an epidemiologic study of a family on 3 of whose 4 members false positive serologic reactions to the tests for syphilis were obtained simultaneously. These tests were traced as presumably originating from a mild upper respiratory infection. Among a small number of contacts exposed to the same infection as the members of this family, there was evidence that suggested that they were immunologically similarly affected.

Syphilitic Reagin in Normal and Apparently Non-syphilitic Human Blood and in Animal Blood. It has been shown that the serum of many apparently normal persons may show measurable or even important amounts of the reagin or reagin-like substances responsible for biological false positive reactions.[272] It has also been demonstrated that the serum of a number of animals gives, in varying percentages, positive results to serologic tests for syphilis even though the animals are known to be demonstrably incapable of inoculation with the disease. This latter fact should not, as Kemp, Fitzgerald and Shepherd[157] have indicated, be regarded as evidence of unreliability of serologic tests for syphilis in man. Many observers have shown that complement fixation techniques can be so modified, for example, that they are always negative in non-syphilitic rabbits and regularly positive at the height of the infection in syphilitic rabbits, notwithstanding the fact that a certain proportion of rabbit serums react positively to complement fixation tests for syphilitic reagin under certain modifications of technique The whole subject of positive serologic reactions for syphilis in animals is well reviewed by a number of authors.[51,85,104,105,157,252,273,274] The cause of this positive reaction in animals is not known. The absence of heterophil antibodies in the cow, as demonstrated by Greene and Harding,[104] indicates that the substance which gives rise to positive Kline reactions is different from that present in the serums of patients suffering from infectious mononucleosis.

In 1931 Malloy and Kahn[195] succeeded in showing that when normal serum is mixed with standard Kahn antigen, microscopic aggregates gradually form. They were able to establish quantitative relations between the areas of aggregation developed during various periods of exposure for normal serums and for syphilitic serums mixed with a standard and a sensitized Kahn antigen as used in the Kahn presumptive test. As the authors put it, "It appears that the difference between non-syphilitic and syphilitic serum is one of degree rather than of kind; that it is quantitative rather than qualitative." What occurs in syphilis is the increase of a lipoid aggregating quality possessed nonetheless even by non-syphilitic serums. In 1942 Kahn and his associates[147] showed that the number of non-specific sensitivities of a serodiagnostic test for syphilis can be readily

increased by various modifications of the test. The use of excessively sensitive antigens may result in as high as 40% of false reactions. The use of such antigens combined with the performance of the tests at 1° C. may result in about 89% of false positive reactions. If, in addition, unheated serums are employed (instead of serums heated at 56° C. for 30 minutes) the non-specific sensitivity may approach 100%.

Pierce and Breazeale[239] summarize experiments with plant saps and adsorbents such as calcium and sodium zeolite in which they find evidence that "reagin" is a divalent sodium or magnesium cation participating in a base exchange reaction. The beef heart antigen acts as a zeolite in producing a floc. The work is as yet unconfirmed. Barnes and his coworkers[7] have suggested from their work that even diet may play a part in non-specific reactions, since in some cases positive reactions have become negative promptly following the use of a meat-free, milk-free, abundant liquid diet. The effect of alcohol ingestion on serologic reactions is one debated for a long time. Brittingham and Rosen[33] thought the influence of this agent was overestimated. It had no apparent effect on various serologic tests in patients with untreated syphilis. In 1935 Hoversen, Peterson and Sackett[132] even claimed that meteorologic variations affect the outcome of the serologic tests for syphilis. This has been denied by Kelley and Short[155] and, although Greval[107] noted such a seasonal variation, he felt that it was due to defects in the complement. Schreus and Foerster,[268] as well as Barnett, Jones and Kulchar[8] devised methods and accomplished the demonstration of syphilitic reagin present even in the serums of non-syphilitic individuals. Later Barnett, Kulchar and Jones[9] found, in confirmation of the pioneer study of Strickler, Munson and Sidlick[291] that an injection of neoarsphenamine to non-syphilitic subjects caused a definite increase in reagin-like substance in their serums. Lund,[191] using a method of flocculation employing maximal serum proportions with secondary recovery of antigen, succeeded in demonstrating the presence of reagin in normal serums. Sherwood, Bond and Canuteson[272] demonstrated a positively reacting substance in the blood of 13 of 1017 healthy students. In an elaborately conducted and controlled survey of 40,545 students' serums Eagle[71f] estimated the incidence of one false positive reactor in every 1125 students as the probable normal for the biologic false positive. Statistically corrected for other considerations, this proportion fell to 1 in every 4000 persons tested. In a similar study, Greene, Breazeale and Andes,[103] using the Kahn and one of a number of other flocculation procedures, found 1.66% positive or doubtful non-specific reactions among a carefully studied group of 5000 college students. Mohr, Moore and Eagle[206] have recently reported 9 normal persons yielding biologic non-specific reactions.

Among hospitalized patients, various estimates of the incidence of false positive reactions have been given. Crawford and Ray report 0.42%,[54] Clifton and Heinz,[48] 1.46% (children); Hill,[127] 0.14% repeatedly positive and became negative within 1 week to 9 months without treatment; Forssman,[87] 0.13%; Eldh,[76] 0.25%; Krag,[173] 0.027%, and Krag and Lønberg,[174] 0.04%. Davis,[57] who has compiled the statistics from the literature, feels that the Scandinavian authors have reported so low an incidence because of the stringent criteria used. Lynch,[192] in an interesting report, stated that "even in good laboratories the number of doubtful or conflicting reports may equal the number of significant strongly positive reactions." On a series of 2764 patients recently admitted to the University of Minnesota Hospital, "the incidence of subsequently diagnosed syphilis

was nearly 1.5%, but misleading serologic reports were obtained in 2% of the whole group. When there is clinical evidence of syphilis, it is obvious that partially positive serologic reports are probably significant, but in the absence of other demonstrable evidence one must look askance at reports of 1, 2, or 3 reactions even on multiple specimens. One must also be suspicious of falsity when on the same specimen positive reactions by one technique are accompanied by negative reactions to another."

The daily variation of reagin content of syphilitic serum has long been regarded as a basis for the fluctuating and alternating positive and negative reactions in serial tests on syphilitic and non-syphilitic individuals.[52,101,289c,301] If the work of Mohr and Smith[208] is confirmed, a large part of this clinically recognized daily variation will have to be assigned to the category of technical rather than biologic error or variability. Mohr and Smith[208] showed by collecting and freezing a series of sera that the variability in reaction as between individual successive specimens practically disappears when a series of frozen specimens is examined at one and the same time. Daily variability in serologic results is probably the result primarily of daily fluctuations of the sensitivity of the tests employed. (*Cf.* Stern,[287] Haller,[114] Meirowsky,[202] Meier,[201] Eagle,[71e].) This periodic variability of serologic outcome must not be forgotten in evaluation of clinical material. Attempts have been made to produce false positive Wassermann reactions artificially by the addition of certain chemicals to negative serums. These reactions, strictly speaking, cannot be classed as biologic, but may throw some light on the causal mechanism of biologic false positives. Owen, Brooks and Tucker[228] tried cholesterol, potassium, calcium, tannic acid (in bottle corks). None of these produced a positive reaction. Tannic acid or acetic acid added directly to negative serums did produce a positive reaction. Eagle,[71a] in an earlier study, was unable to make an originally negative human serum Wassermann-positive by physical or chemical treatment. Breazeale,[30] in a series of papers, showed that certain physical manipulations, *e. g.*, ultraviolet light, diathermy, and so forth, could change serum reactivity. Rytz,[258a] in 1935, was able to obtain strongly positive Wassermann and flocculation reactions in rabbits by injecting intravenously the flocculate obtained from human syphilitic serum. Becker[13] confirmed this phenomenon in rabbits and showed, in addition, that this human syphilitic flocculate was antigenic because 10 times as much flocculate was obtained as the amount injected into the rabbit.

Diseases and Other Conditions Responsible for Biologic False Positive Reactions.

Yaws, Bejel and Pinta. These 3 treponematoses described as "syphilis-like," "syphiloid" or actually syphilis, are all caused by organisms indistinguishable from *Spirochæta pallida*. In the strict sense, positive serologic reactions occurring in these diseases should not be considered as false, but true positives. In view of the fact that they are of importance mainly in the locales where they are endemic, and the fact that they respond to antisyphilitic therapy, differentiation from venereal syphilis is of little practical importance. The serologic findings in bejel have been reviewed by Hudson,[134] those in pinta by Beerman,[14b] and those in yaws by Maltaner.[196]

Leprosy. A survey of the literature on the incidence of biologic false positive reactions in leprosy reveals that there is a wide variety of figures,

but the trend is generally toward a high percentage. Some believe that this may be due to the occurrence of a high proportion of syphilis and yaws among lepers (Hazen *et al.*[119]). Howard Fox[89] was one of the first in this country to point out that a positive Wassermann reaction is frequently obtained in cases of leprosy without history or symptoms of syphilis. Of course, estimates of the occurrence of positive reactions in patients with this disease are conditioned by the type of test employed. For example, Kolmer and Denny,[166] in 1923, reported that in 123 cases studied with the old Wassermann technique, apparently false positive reactions occurred in 7.2% of patients with leprosy, but that the Kolmer modification did not give false positive reactions in leprosy. Eagle and Kolmer[327] applied the Kahn test to 28 patients with leprosy and concluded that in leprosy uncomplicated with syphilis, the Kahn test gave negative reactions. In the United States, the 1934 evaluation study of serologic tests[55] showed that in 50 lepers the Kolmer test gave 64% false reactions, the Kahn test 60%, the Eagle flocculation 72%, the Kline test 66% and the Hinton test 40%. When clinical studies to exclude syphilis and repeated serologic tests were made, only 15 patients (30%) had positive or doubtful reactions to all tests, 8% had negative reactions and 62% showed discordant reactions with the different tests.[119] Some authors claim that there is no relationship between the phase of leprosy and the serologic reactions.[57] Other authors[3,80,130,185,212,236] have related the higher incidence of positive reactions to certain aspects of leprosy, especially the mixed or lepromatous cases. Badger[5] found more positive cases among women.

These considerations, therefore, leave little wonder that various authors have obtained such a variety of results from the application of serologic tests to leprosy.[5,29,80,119,130,137,185,212,215,224,226,248,262,275,283,305,323]

In order to differentiate true from biologic false serologic reactions in lepers, Capelli[39] performed complement fixation tests on the serums of 24 leprous patients using Gaehtgen's phenolized culture[94] of *Spirochæta pallida* (palligen) as antigen, and compared the results with those obtained with the Wassermann procedure and the Meinicke flocculation test on the same serums. He reported that with the spirochetal test none of the serums gave a 4 or 3+ reaction except in 1 patient who was considered to be syphilitic. There were partially positive (1 or 2+) reactions with 22% and negative reactions with 78% of the serums. The Wassermann reactions were positive with 66%, partial with 17%, and negative with 39% of the serums. On the basis of these results, Patrick and Wolfe[236] reviewed cases of leprosy and concluded that when examined with the spirochetal complement fixation test, the serums of non-syphilitic leprous patients show a tendency toward falsely positive results, although to a lesser extent than with the Wassermann and Kahn tests. Eagle and his associates[73] examined a group of lepers' blood and cerebrospinal fluid with the spirochetal complement fixation test and concluded that in partial confirmation of the work of Capelli, this procedure makes it possible to identify as biologic false positive reactions most of the positive Wassermann and flocculation reactions caused by leprosy in the apparent absence of syphilitic infection. Kolmer[165A] on the other hand, stated that the spirochetal antigens give a particularly high percentage of non-specific or falsely positive complement fixation reactions in the blood from patients with leprosy and malaria, just as tissue or lipoidal antigens yield a high percentage of positive Wassermann and flocculation reactions in the blood of patients with these diseases. The Kahn verification test has also been of little if any value in identifying true from false reactions in leprosy.[46]

Malaria. Much has been written about the ability of malaria to provoke biologic false positive reactions with the various serodiagnostic tests. From flat denial of any effect,[165b,c,183,184,264,276] the estimates have ranged to the statement that by means of serially repeated tests[79,160,176] 90 to 100% of malarial patients at some time in the course of the disease had biologic false positive serologic reactions for syphilis. The more frequently the tests are made, the higher the percentage of positive reactions. The reactions in the cerebrospinal fluid do not parallel the blood changes.[176] The difference of opinion as to the incidence of these false positive reactions is probably due to the inability to exclude the coëxistence of syphilis and other syphilis-like diseases such as yaws which usually gives positive serologic reactions. Most of the positive serologic reactions in malaria occur between the 7th and 21st days of the malarial seizure. Kitchen, Webb and Kupper[160] found that the highest percentage of positive reactions occurred during the period 15 to 21 days after the last previous paroxysm. The greatest number occurred between the 15th to the 21st day after inoculation of induced malaria and most of the positive reactions had disappeared by the 4th week.[36] Kitchen and his co-workers[160] noted that *Plasmodium vivax* infections gave more positive reactions than *Plasmodium falciparum*. Hazen and his co-workers[120] found that the highest proportion of biologic false positive reactions occurred in females. Eagle, Mays, Hogan and Burney[74] stated that the spirochetal complement fixation test was of little value in the serologic differentiation of syphilis and malaria. Kolmer[165g,h] concurs in this view, since spirochetal antigens give a particularly high percentage of non-specific reactions in malaria just as tissue or lipoidal antigens. The Kahn verification test did not always give a consistent reaction in patients with malaria at the hands of Chargin and Rein[46] but DeGroat[63] believed his study showed that the verification test can be employed as an aid in establishing the differential diagnosis of malaria and syphilis. Rosenberg,[255] from his study of this problem, concluded that the Hinton flocculation test for syphilis yields the smallest proportion of falsely positive reactions in malaria of any of the widely accepted serologic techniques. The pattern of positivity in malaria, *i. e.*, positive Kahn and Mazzini reactions, doubtful Kolmer and Kline reactions and negative Eagle and Hinton reactions, can usually be differentiated from that of syphilis. Persistence of positivity by any test beyond 6 weeks in the absence of continued evidence of malaria should arouse suspicion of syphilis.

There is no established explanation for the cause of the false positive reaction in malaria. Eller[77] pointed out that the nature and the regularity of appearance of a positive Wassermann reaction in certain stages of inoculation malaria leads to the assumption that the processes which bring about a positive serologic reaction are similar to those in syphilis. Fischer and Gunsberger[84] believed that the positive Wassermann reaction was due to specific antibodies against erythrocyte lipoids. Among 28 serums obtained from malaria patients, there were 21 with definite to completely positive complement fixation with erythrocyte extract (malaria antigen). With few exceptions, 500 Wassermann negative serums from healthy persons and patients reacted negatively. There were some among 60 Wassermann positive syphilitic serums which also reacted with the erythrocyte extract, but these could be differentiated from those of malaria patients by considering the quantitative reaction to erythrocyte extract and Wassermann extracts. When both reactions are tested for simultaneously, the authors believe malaria may be differentiated from syphilis.

XUM

For the interested reader, there are numerous reports on the influence of malarial infections on the serologic reactions.[36,55,56,60,63,83,106,118,124,160,203,221–222,233,234,235,248,255,322,398]

Pneumonia and Respiratory Infections. There has recently been a rising interest and appreciation in this country and abroad of the importance of respiratory infections and pneumonia as a cause of biologic false positive serologic reactions. Eldh[76] in 1932 made serologic studies on 20,798 medical patients and found that 52 of them had probable false positive reactions. Twenty-six of these 52 patients had pulmonary disease and there were 10 cases of pneumonia (out of 1014 cases of the disease), 6 emphysema, 7 tuberculosis and 3 influenza (out of 548 cases so diagnosed). Other authors, especially from Scandinavia, have reported cases of respiratory infections with transient positive serologic reactions. Krag and Lønberg[173,174] of the Danish Serum Institute, in testing the serums of 120,000 presumably non-syphilitic patients, uncovered 53 patients (0.04%) with biologic false positive serologic reactions for syphilis. Of the 53, 60% were from patients with respiratory infections. Boas and Neergaard[23] reported on 1 case of bronchopneumonia and 2 with bronchitis with false positive reactions. Kissmeyer,[159] who reported 10 cases with biologic false positive serologic reactions for syphilis, had 2 patients with pneumonia among them. Similar reports of false reactions in pneumonia were reported by Forssman,[87] Krag,[173] Munch-Anderson,[216] Gigante,[96] and Jahnel.[139] Stryjecki stated in 1938[292] that about 5% of patients with pneumonia have biologic false serologic reactions for syphilis. Lindau[182] noted 10 transient positive cases of respiratory infection. Among his cases were 4 members of a family of 5 suffering from bronchitis. Clifton and Heinz,[48] using the Kolmer Wassermann, the Kahn and the Eagle tests in a survey of prenatal syphilis in a hospital for sick children, found an incidence of 1.46% of false positive reactions, a majority of which were obtained from patients with respiratory infections. Mohr, Moore and Eagle[206] found a rather high incidence of respiratory disease among their patients with false positive reactions. They also reported 2 patients with sore throats and 1 of labyrinthitis of unknown cause, in all of whom false positive serologic reactions appeared. Allen Hill[127] noted 242 non-specific reactions (positive and doubtful) among 26,700 Hinton and Davies-Hinton microflocculation tests from the records of the in-patient and out-patient services of the Infants' and Children's Hospitals of Boston. Of these tests, 114 obtained from 37 patients represent false positive and false doubtful reactions which were proved. The remaining 128 tests are single positive or doubtful results which may be either non-specific reactions or the consequence of laboratory or clerical error. Respiratory infections in particular, and acute infections in general, make up a major portion of the non-specific reactions noted in Hill's study. Bridgeman and Jacobson[32] also reported such cases in children.

In 1936 Fanconi[81] reported a clinical picture for which he suggested the name "pseudoluetic, subacute, hilifugal bronchopneumonia of poor children." This was associated with false positive reactions to the serologic tests for syphilis. In 1941, Hegglin and Grumbach[122] published observations on a similar disease in adults under the designation, "Das Wassermann-positive Lungeninfiltrat." They studied, among other things, the frequency of non-specific Wassermann reactions in pneumonia, bronchopneumonia, and pulmonary tuberculosis in the medical clinic in Zurich in the years 1938 to 1940. Among 680 pneumonia and bronchopneumonia patients there were 19 with non-specific serologic reactions (2.8%), and

among 403 cases of pulmonary tuberculosis 13 (3.2%). The authors called attention to the fact that these were cases with a weak or doubtful Wassermann reaction, or cases where only the Kahn or Citochol reaction was observed in only 1 case, died shortly thereafter, and no evidence for syphilis could be found at autopsy. In the same year, Benedikt[17] encountered 7 definite and 1 possible additional cases of this "pseudoluetic pneumonia" in the Children's Hospital of the University of Zurich. Grumbach[109] found *Hæmophilus pfeifferi* as the sole organism in the sputums of 6 cases. In an animal study, it appeared that the Wassermann, Kahn and Citochol flocculation negative rabbits by immunization with the influenza bacillus of Pfeiffer became Wassermann and flocculation positive, and the strength of the agglutination titer went parallel with the intensity of the Wassermann reaction. This was felt to indicate that the influenza bacillus, like alcoholic tissue extracts, possesses a fraction like *Treponema pallidum* which calls out a positive reaction for syphilis. However, 42 cases (25 pneumonia, 13 grippe, 4 "grippe-pneumonia") with positive agglutination for influenza bacillus, yielded negative Wassermann reactions. Also, in 2 cases of influenza (Pfeiffer) meningitis, the Wassermann and flocculation reactions were negative.

While there is no definite reason to call these cases from Switzerland virus pneumonia, the symptomatology, as described by Fanconi,[81] are very similar to the so-called "primary atypical pneumonia of unknown etiology." In reports of known atypical pneumonia, there has been suggestion, though scant mention, of the possibility of biologic false positive reactions in tests for syphilis.[66,162] Major Charles R. Rein, Chief of the Division of Serology, Army Medical School, in a personal communication to Kolmer[165i] stated that 10 cases in 50 have shown false positive reactions after the 12th day of the disease, the majority disappearing or reacting negatively in 2 to 6 months. In a later communication, Rein and Elsberg[248] studied a group of 72 patients with primary atypical pneumonia with radiologic evidence of pulmonary involvement. These patients were subjected to serologic examination as soon as possible after hospitalization. In most of the patients the first symptoms were malaise, cough and elevation of temperature 5 to 10 days prior to hospitalization. Weekly repetition of the serologic tests was attempted, but in 42 (58.3%) only a single serologic examination was possible. Of the 72 patients, 17 (23.6%) gave positive serologic reactions with 2 or more tests in the Army serodiagnostic battery. Ten patients gave low titered positive reactions, while 7 of them gave strongly positive serologic reactions. The majority of these individuals became seronegative within 3 months after the onset of the illness.

Cold agglutinin tests were also done on the serums, from these patients, but there did not appear to be any direct correlation between the false positive serologic reactions and the positive cold agglutinations.

Serums of 36 patients in this group were also subjected to a complement fixation test for psittacosis and here, again, there was no relationship between the false positive reactions for syphilis and the false positive psittacosis reactions.

Of 79 patients with miscellaneous upper respiratory infections, including influenza, bronchitis and lobar pneumonia, similarly investigated, 20.2% gave false positive serologic reactions for syphilis and positive cold agglutination tests were much lower in titer than those obtained in the primary atypical pneumonia group.

Loveman[188] felt that in his 100 cases of false positive serologic reactions for syphilis, Army immunization played a greater rôle than did upper

respiratory infections. Davis,[57] in his exhaustive review, calls attention to the interesting fact that Gigante[96] suggested that false positive reactions in pneumonia might be related to the herpes virus according to Koch's concept but "such an explanation appears unlikely since the activating herpes in pneumonia is extremely common." He also calls attention to the fact that while false positive reactions may occur in various upper respiratory diseases, undoubtedly some of the reported so-called upper respiratory infection cases may have been undiagnosed infectious mononucleosis.

Infectious Mononucleosis. Infectious mononucleosis (glandular fever) is a disease which has aroused much interest in the internist. To the syphilologist, it is of special importance because the symptomatology, so much like secondary syphilis[187,261] may be accompanied by positive reactions in the serologic tests for syphilis. This association of biologic false positive reactions and infectious mononucleosis has been the subject of special reports[20,117,154,167,204,261,263,315] and has been deemed deserving of mention in general articles on infectious mononucleosis,[20,38,88,97,113,136,231–232,241,243,310,312,317] or papers devoted to discussion of biologic false positive reactions.[57,165i] Others have, however, denied that this disease may be associated with false serologic reactions. Löhe and Rosenfeld[187] were apparently the first to note the fact that a transitory positive Wassermann reaction may sometimes appear during the course of infectious mononucleosis ("monozytenangina"). Parkes-Weber,[231] however, was actually first to call attention definitely to the fact that temporarily positive serologic reactions for syphilis may occur in glandular fever.

Attempts at estimating the actual incidence of false positive serologic reactions in this condition have been made by various investigators. Sadusk[261] felt that the reports suitable for analysis would indicate that approximately 15% of such patients present a temporarily positive syphilis serology during the course of their illness without any history of manifest evidence of syphilis, though it is possible that a much higher incidence may be found in future studies by the performance of serologic tests more regularly and persistently. For example, in 1939, he found 8% of 37 cases in which 1 or more serologic tests for syphilis were applied, but in 1941 he found 13% of 45 patients. This increase was due to the fact that in the additional 8 patients the serologic tests for syphilis had been repeated at regular intervals. Other estimates of the incidence of positive serologic reactions in this disease are: Gooding,[97] 60% of 27 cases; Bernstein,[20] 16% of 37 cases. Kolmer, Ginsburg and Lynch[167] collected 191 cases from the literature and found an incidence of 20.9%. Their own series of 18 patients, 16 of whom had only 1 test, gave completely negative reactions to the Kolmer quantitative complement fixation and Kahn standard flocculation tests, but the Kline diagnostic test gave 1 positive and 1 doubtfully positive reaction in the group. In a later review, Kolmer[165i] showed that the incidence of reactions reported by various investigators has varied all the way from none[204,205] to 100%, with an average of 7.3% doubtful or positive complement fixation reactions in 202 cases and 9.6% doubtful or positive flocculation reactions in 157 patients.

Usually the false reaction appears during the 2nd week of the disease and, according to Sadusk[261] may rarely appear during the latter part of the 1st week. It usually becomes negative within 2 weeks, but may persist longer (2 months;[261] 3 months[170]). The titers of the reactions in infectious mononucleosis are usually lower than those in secondary syphilis.

Various explanations have been offered for the occurrence of the false

serologic reactions in infectious mononucleosis. Nonetheless, the mechanism is actually unknown. Werlin, Dolgopol and Stern[317] believed there was no correlation between the titer of the heterophil antibody reaction and this false positive tendency (*Cf.* Bernstein[20]). Warren[312] felt that falsely positive Wassermann, Kahn and Eagle reactions were frequent in infectious mononucleosis and proposed two mechanisms for these findings: (1) the antibodies may be those normally present or previously acquired in some manner; (2) the chemical and spatial structure of the antigens of various diseases giving non-specific reactions (typhoid, paratyphoid, undulant fever) and infectious mononucleosis may be very closely related.

It was early stated that reagin, the substance responsible for positive syphilis serologic reactions, was not responsible for the occurrence of the positive Wassermann reaction in infectious mononucleosis. This was based on the occurrence of negative Kahn reactions. This argument is invalidated by the consequent observation of the simultaneous occurrence of both positive Kahn and Wassermann reactions in a patient. Furthermore, Kaufman[154] had among his patients with infectious mononucleosis, 2 seronegative treated congenital syphilitics. The Wassermann reaction did not revert to positive in either during the course of the infectious mononucleosis. Sadusk[261] noted two peculiarities of false positive serology in infectious mononucleosis and suggests that whatever is responsible for the positive reactions is not reagin. These peculiarities are negative flocculation and positive Wassermann, and in 1 case the Wassermann reaction was more strongly positive with the alcoholic than with the cholesterolized antigen. Saphir[263] has invoked the idea of a change in the blood proteins (*Cf.* lymphogranuloma venereum) as the responsive factor. Sadusk's[261] study of 2 patients did not sustain this view. It has been suggested that these reactions may be due to a reaction between heterophil antibody in the serum and heterophil antigen in the alcoholic extracts of mammalian tissues employed in these tests.[117,285] This view is considered untenable by Kolmer[167] and his associates on the basis that the positive reactions should occur only in the complement fixation and flocculation tests employing extracts of the tissues of certain animals known to contain heterophil antigen, whereas negative reactions should occur in tests employing extracts of tissues of animals regarded as free of heterophil antigen.[38] The Kolmer antigen, for example, is prepared of beef heart (1 of the animals known to be free of heterophil antibodies). While Kolmer, Ginsberg and Lynch[167] as well as Mills and Jahn[204] found infectious mononucleosis to give consistently negative results, positive results to flocculation tests performed with beef heart antigen have been encountered by various authors.

Kolmer[165d] carried out studies to determine whether or not *Listerella monocytogenes* could produce in rabbits the reagin or antibody-like substance responsible for the Wassermann and various flocculation reactions which occur in syphilis. Intravenous immunization of rabbits with living and heat-killed avirulent strains did not produce complement fixing or flocculating reagins for antigens commonly used in the serodiagnosis of syphilis, and also did not produce agglutinin for sheep erythrocytes in the immunization of rabbits. Davis,[57] in his masterful review, cited the following conclusive evidence against the relation of the heterophil antibody to sheep cells to biologic false positivity: (1) flocculation tests are also frequently positive, although antisheep cell hemolysin plays no rôle in these; (2) there is no correlation between the heterophil antibody titer and serologic tests;[20] and (3) absorption of a few such sera with sheep cells has

removed the heterophil antibody without appreciably affecting the serologic tests.[20,117,167]

Vaccination and Immunization. Because of the serious implications of positive serologic reactions, true or false, in military personnel, the fact that routine procedures such as vaccination and other immunization procedures may induce biologic false positive reactions to blood tests for syphilis makes it necessary to ascertain the extent and character of this phenomenon.

In 1940 Barnard[6] first modestly reported a patient whose blood showed a series of positive reactions for syphilis following successful vaccination for variola. The positive reactions persisted for more than a month. Some doubt has been raised that vaccinia caused the positive reactions in this case because the "primary take" did not appear until nearly 3 weeks after vaccination, but the evidence submitted was reasonably conclusive that vaccinia was the causative factor. Barnard[6] also mentioned that Giordano discussed a similar case in 1935. In 1941 Giordano also informally reported to Lynch and his co-workers[193] that he had observed another person who had a false positive serologic reaction associated with vaccinia. In each case the strongly positive reaction gradually changed to negative within 45 days. In 1940 Bay and Sankstone[10] reported that because they had examined 100 serologically negative persons both before and after vaccination, with negative results, they concluded vaccination was not an important cause of false positive reactions. Mohr, Moore and Eagle[206] also reported a case among their patients yielding false positive reactions. Thomas and Garrity[302] also investigated this problem and in 2 reports which include 20,000 Kahn tests made on recruits entering the Naval Training Station, San Deigo, between July 1939 and January 1941. All the tests were run by the same technicians. In the entire series of 20,000 there were 73 (0.365%)* positive initial Kahn reactions, of which 32 (0.16%) proved to be false positives and 41 (0.205%) were persistently positive. Of the 41 positive cases, 10 were definitely believed to have acquired syphilis, 3 to have congenital syphilis; 20 probably had the disease, and 8 were exceedingly doubtful. Of this group, of positive cases, 65% had had promiscuous relations with prostitutes, 28% had had few sexual contacts, and 7% denied sexual intercourse. The findings suggest a definite relationship between cowpox vaccination and the false positive test. In the first 10,000 tests the blood was taken after vaccination; in this group there were 26 false positives. In the second 10,000 the blood was taken before vaccination and there were only 6 false positives. One particular case in the second group is cited. This recruit had a negative Kahn reaction on arrival and 3 weeks after vaccination a strong positive which persisted for 3 weeks, since which time it has remained negative. No relationship between antityphoid inoculation and the false positive Kahn test could be found. Several recruits from the Southern Gulf States developed clinical malaria after their arrival, and all of these had positive Kahn tests at some time during their treatment. The tests which were found to be falsely positive became negative within a period of 4 weeks.

Lynch, Boynton and Kimball[193] demonstrated conclusively that smallpox vaccination was a frequent cause of false positive reactions. In a careful and well-controlled study of 263 persons with a primary vaccinia they obtained an incidence of 16% positive individuals by one or more

* This figure corresponds to that obtained by Barnard[6] who had 4 positive reactions among 1116 male college students of about the same age and geographic distribution of the naval recruits.

of the Kolmer, Kline, Hinton and Mazzini tests. The intensity of the reactions varied from doubtful to 4+ and in most cases they appeared in 2 weeks and remained positive for 2 months. Several of the positive reactions persisted for 4 to 5 months. Individuals with accelerated or immune reactions were not included in this study. The Kahn verification reaction was of the syphilitic type in the only case in this series in which this procedure was performed. The authors felt that the recognition of the highest possible number of false positive reactions would require the performance of tests on specimens collected more frequently through the period from 2 to 6 weeks after vaccination. This procedure might have yielded a different figure than the 16% recorded.

Arthur and Hale[4] found that 14 of 94 soldiers (14.8%) gave a temporary false positive reaction after smallpox vaccination. These same men also had been recently vaccinated against typhoid fever, tetanus, smallpox and yellow fever. These authors believed that the false reactions were the result of the combined inoculations of the routine Army immunizations. Lubitz,[190] in 1943, found titers as high as in syphilis in individuals vaccinated, but the reactions disappeared quickly (2 to 17 days) on storage at 4° C. They were negative 14 to 104 days after vaccination. Positive reactors failed to give the heterophil antibody test. In another study of 100 unhospitalized individuals with a primary smallpox vaccination be obtained 13% positive reactions to 1 or more tests.

Favorite,[82a] in 1943, had an opportunity to make a study similar to that of Lynch and his co-workers.[193] Importation of a case of smallpox near the Philadelphia area led to mass vaccination of approximately 1,000,000 persons. He selected a group of 202 individuals who had had a serologic test for syphilis within a reasonable time previous to vaccination. Their ages ranged from 3 weeks to 84 years and over half of them were between 20 and 30 years of age, and consisted mostly of medical students and nurses. Of these individuals, 44 developed a primary cutaneous (non-immune) reaction at the site of inoculation, 134 developed a local accelerated (vaccinoid) form, and 24 were immune. Of the 202 individuals on whom a single blood examination was performed 19 were found to be positive by 1 or more of the Kolmer simplified complement fixation tests, the Kahn and Mazzini flocculation tests. They were examined from 10 to 57 days following vaccination, but 93.6% were done before the 43rd day. Of 24 persons who gave a negative reaction 14 days after vaccination and were reëxamined 14 days later (1 month after vaccination), 4 were now positive. Favorite[82] believed more positives would have been found if the entire group had been examined in a similar manner. In all, 24 of 202 (11.8%) gave a false positive reaction for syphilis. The reactions were about equally divided between the non-immune and accelerated groups. Since none occurred in the immune, the percentage would have been higher if this group were excluded. The reactions were usually 2+ or less (negative or doubtful) but 22.4% were 3+ or stronger. Only 8 were still positive at the end of 60 days; 4 were weakly positive in 80 days and 2 persisted for 100 days. By 120 days all were negative.

In 1944 Favorite[82b] was able to make a second study of this problem. The entire student body of a medical school was vaccinated against smallpox in January 1943. Subsequently, a new freshman class was enrolled, leaving three-fourths with a recent vaccination. Six months later the students were again subjected to vaccination, not only to smallpox, but to typhoid, paratyphoid fever and tetanus. Since smallpox vaccination was given after the administration of typhoid vaccine and 2 injections of

tetanus toxoid, an opportunity was offered to determine just what rôle such immunization played in the production of false positive reactions for syphilis. It also offered additional data for the continued study of smallpox as a cause of false positive reactions. Other factors were also studied.

The second group included 323 men between the ages of 21 and 30 years, three-fourths of whom were vaccinated for smallpox 6 months previously. Following a preliminary blood test, they were revaccinated. Six individuals developed a primary cutaneous (non-immune) reaction, 71 developed an accelerated (vaccinoid) form, and 246 were immune. One month after the date of vaccination, a blood specimen was obtained and examined with the Kolmer, Kahn and Mazzini tests. No opportunity was offered for more frequent and prolonged observations. The results of the study showed that smallpox (vaccinia) vaccination followed by an accelerated or primary (non-immune) cutaneous response causes at least 11 to 16%. An immune response to smallpox vaccination can be disregarded as a significant cause of a false positive reaction.

The false positive serologic reactions for syphilis are transitory, appearing within 2 weeks of the date of vaccination and disappearing in most instances, within 2 months or persisting occasionally as long as 4 months. Typhoid (T.A.B.) and tetanus toxoid immunizations have no significant bearing on the production of false positive serologic reactions for syphilis. Favorite's[82] study also suggested (*a*) that recently vaccinated individuals who gave a positive serologic reaction do not have a reactivation of their positive reactions following typhoid and tetanus immunizations 5 months later, and (*b*) individuals with a false positive serologic reaction, when revaccinated for smallpox within 7 months, may again present a weak serologic false positive response for syphilis, even though the second vaccinia reaction is of the immune type. Positive serums stored in the ice-box at 40° C. for 7 months have a variable loss of titer. This loss is not sufficient to be of differential diagnostic value.

Heimoff,[123] on the basis of 8 cases, believes that tetanus toxoid stimulating doses ("booster shots") are apparently capable of causing biologic false positive reactions.

Loveman,[188] on the basis of 100 cases of false positive serologic reactions for syphilis, thought that the reactions were probably the result of both routine Army immunizations and upper respiratory infections, but that the former played the more important rôles.

A most significant study of this problem is that by Rein and Elsberg.[248] Because it summarizes the essential facts regarding the relationship between vaccinia and biologic false positive serologic reactions for syphilis, it is cited *in toto*.

"**Vaccinia.** A group of individuals who received routine smallpox vaccinations were examined 1 week later. Eighty had developed vaccinia and 49 had developed vaccinoid reactions. Blood specimens were obtained from these 129 individuals for serologic examination. This was repeated at weekly intervals. All serums were subjected to a battery of 6 serodiagnostic tests including the Kline Diagnostic, Kline Exclusion, Boerner-Jones-Lukens, Mazzini, Kahn and Kolmer procedures. There were 58 (44.9%) who developed doubtful and positive serologic reactions with 1 or more tests in this serodiagnostic battery. In this group of serologic reactors, 50 (86.2%) developed their first positive serologic reaction between the 8th and 14th day following the vaccination. Three (5.1%) developed the first positive serologic reactions on or before the 7th day and 5 (8.6%) developed the first positive serologic reaction between the 15th and 21st day following the vaccination.

"Of the 80 individuals with vaccinia reactions, 41 (52.2%) developed false positive blood tests, whereas of the 49 individuals with vaccinoid reactions, 17 (34.7%) developed false positive blood tests.

"This would seem to indicate that false positive tests will occur more frequently in individuals with vaccinia reactions, as compared to those with vaccinoid reactions. It should be pointed out, however, that the incidence and titer of the false positive serologic reactions was not entirely influenced by the type of severity of immunologic response to the vaccine virus. It was observed that many individuals with marked vaccinia reactions associated with axillary adenopathy remained serologically negative throughout this investigation, while other individuals with slight vaccinoid reactions developed high titered false positive serologic reactions. It would appear, therefore, that certain individuals ('serologic reactors') were more likely to develop positive serologic reactions than others, and the type of vaccination reactions was of only secondary importance. It is also true, however, that in a group of individuals who are 'serologic reactors,' the incidence and titer of the serologic reactions will be much higher in the vaccinia than in the vaccinoid group. Furthermore, there is some evidence to suggest that these serologic reactors will develop false positive blood tests as a result of other non-syphilitic conditions.

"Similar investigations were carried out in individuals who received 3 typhoid immunizations at weekly intervals and 3 tetanus immunizations at 3-week intervals. Although the series was too small to warrant any definite conclusions, it seemed that the incidence and titer of false positive serologic reactions was relatively insignificant."

(*The latter half of this article, with references, will be published under Dermatology and Syphilology in the October issue*)

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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THE TONSIL-ADENOID PROBLEM

By Noah D. Fabricant, M.D.

Relegated for some time to a scientific exile and characterized by a notable decrease in the number of articles published, there has been a recent breaking out afresh of interest in the subject of tonsils and adenoids. This recrudescence has been channelized in three major directions: the medico-surgical aspects, never comprehensively established; the relation of tonsillectomy to poliomyelitis; and the application of irradiation to hypertrophied lymphoid tissue in the nasopharynx as a means of treating certain types of impairment of hearing.

Medico-surgical Aspects. According to Reimann and Havens,[17] the causative relationship of infections about the teeth and tonsils to systemic disease is unproved and the removal of teeth and tonsils in an effort to influence the course of systemic disease is unjustified in the majority of

cases. Citing the criteria for the diagnosis of chronically diseased tonsils, they point out that local evidence of disease frequently disappears if recovery from the general disease ensues and that tonsils, particularly in malnourished, underweight or otherwise subnormal children, probably would become "normal" in appearance spontaneously if the general health were improved by hygienic measures. They believe, further, that large groups of persons whose tonsils are present are no worse off than those whose tonsils are out; that patients whose teeth or tonsils are removed often continue to suffer from the original disease for which they were removed; that beneficial effects can seldom be ascribed to surgical procedures alone; and that beneficial effects which occasionally occur after surgical measures are often outweighed by harmful effects or no effect at all.

"When should the tonsils be considered a menace to a child's development?" asks Kaiser.[14] In a study of 4400 children over a period of 10 years records were kept of the incidence of common infection of the upper respiratory tract, bronchitis, pneumonia and the various manifestations of rheumatic infection. Tonsillectomy was advised for all of the 4400 children, but only half of the group submitted to the operation; and none of the children in the control group of 2200 were operated on during the succeeding years. Kaiser found that markedly hypertrophied tonsils and tonsils that are repeatedly inflamed, giving rise to attacks of tonsillitis and cervical adenitis, often impair normal physical development and that such infections as the common cold, otitis media, sinusitis and laryngitis may unfavorably influence the child's normal development. But he was unable to demonstrate that tonsils frequently are a causative factor in these infections. Removal of tonsils does not seem to reduce the incidence of bronchitis, pneumonia or tuberculosis. By reducing the number of infections of the throat, tonsillectomy appears to benefit the rheumatic child. He concludes that in approximately 20% of children the tonsils are either hypertrophied or diseased sufficiently to have an unfavorable influence on the development of the child and that such tonsils should be removed.

Paton[16] carefully studied a series of 909 school girls over a period of 10 years, the decade of the 1930's. Of this group, 516 had their tonsils removed and 393 had not. By comparing the two groups and employing the non-operated group as a control approximating normal, he attempted to provide data which would indicate the effect of operation as related to future health. He found that the group operated upon was no healthier than the control group on arrival at school; while at school, the group operated upon was less healthy than the control group, as shown by the number of school days lost through illness. The group operated upon suffered less from tonsillitis but was more subject to respiratory infections, and lost more days from bronchitis alone than they gained in respect to tonsillitis. When the small groups on whom a single operation was performed (tonsil operation, 57 cases; adenoid operation, 24 cases) were considered, two deductions were arrived at. First, removal of tonsils is the factor in the combined operation responsible for the reduction in tonsillitis and for the increase in respiratory infections; second, removal of adenoids appears to be followed by certain definite effects. Adenoidectomy alone reduces the liability to respiratory infections, but in the combined operation group, the removal of adenoids failed to counteract the increase in respiratory infections which resulted from the tonsillectomy. Removal of adenoids increased the liability to acute otorrhea, while recurrent attacks were seldom prevented. In general, many of these findings appear to

support the contention made in England more than a decade ago that a large proportion of the tonsil and adenoid operations now done in children are "unnecessary, entail some risk, and give little or no return."

In the management of frequent colds, sinusitis, bronchitis and recurrent pneumonia Hansel and Chang[12] stress the possibility of allergy as an etiologic factor. Of 200 children considered as a routine for removal of the tonsils and adenoids because of these complaints, a diagnosis of nasal allergy was established in 13%. Removal of tonsils and adenoids in allergic children should not be performed during hay fever seasons, and the indications for operation should be the same as in non-allergic children. Tonsils and adenoids should not be removed with the idea of alleviating allergic symptoms.

Data on school attendance and gain in weight for tonsillectomized and for non-tonsillectomized children were obtained by Ashley[1] who made a study on 1524 school children in a community under average normal conditions of American life. Of the total number, 602 children had previously had their tonsils removed and 922 had not. The tonsillectomized group lost slightly less time from school than did the group of non-tonsillectomized children, but the difference was so slight as to be insignificant. After tabulating the gains in weight, it was found that the total gain was greater for the tonsillectomized group, and that the total gain in weight for the first year in school for the tonsillectomized group was almost twice that for the non-tonsillectomized group.

The indications for tonsillectomy are considered under three classes by Coates and Gordon,[4] namely: conditions within the tonsils; conditions remote from the tonsils; and conditions adjacent to the tonsils. They state that conditions within the tonsils indicating tonsillectomy are: repeated attacks of tonsillitis; abscess within the tonsils; epidemic streptococcic sore throat; tuberculous tonsils; diphtheritic tonsils; hypertrophied tonsils; Vincent's infection of the tonsils; and halitosis due to infection of the tonsils. Conditions adjacent to the tonsils indicating tonsillectomy are: acute catarrhal and suppurative otitis media; chronic suppurative otitis media; middle-ear deafness; labyrinthitis and inner ear deafness; sinusitis; thyroid disease; laryngitis; pharyngitis; cervical adenitis; peritonsillar abscess; acute phlebitis of cervical veins; and ocular diseases. In a discussion of conditions remote from the tonsils that indicate tonsillectomy, a lengthy list of acute and chronic processes traceable to a primary focus of infection is cited. It is maintained that in the management of such infections the closest coöperation of the internist, pediatrician, general practitioner and the otolaryngologist is advisable. The authors scorn injudicious tonsillectomies. Shambaugh[20] believes that tonsils and adenoids should be removed when there is evidence that they are the seat of chronic infection which is producing, or threatens to produce, bodily injury greater than the dangers, disability, discomfort and inconvenience of removal. Emenheiser[7] does not believe that the consistency of the tonsil or the presence of a yellowish secretion in the crypts is a reliable guide in making a diagnosis of infected tonsil. The preservation of the human race or the survival of the fittest, he concludes, does not depend on tonsillectomies.

Relation of Tonsillectomy to Poliomyelitis. Several clinical reports of bulbar poliomyelitis following the removal of tonsils and adenoids prompted Sabin[18] to investigate experimentally its relationship. He found that while mere transitory contact of the virus with the normal or injured pharynx or tonsils of monkeys will not produce poliomyelitis, it is possible

to infect these animals when the virus in quantities of from 100 to 1000 minimal cerebral infective doses is injected into the tonsillopharyngeal region. The high incidence of the bulbar type of the disease among monkeys and evidence that the virus did not invade the central nervous system along the olfactory pathway indicated to him that after tonsillopharyngeal injection the virus progresses along a local peripheral nerve. It is concluded that the season of high incidence of poliomyelitis is an unfavorable period for operations in the upper air passages.

Observations on an occurrence of 5 cases of the bulbar type of poliomyelitis in a family of 6 children following general tonsillectomy were reported by Francis and his associates Krill, Toomey and Mack.[9] The youngest child, but $2\frac{1}{2}$ years of age, was not operated on and did not contract the disease. In an effort to determine the sources of the infection, extensive epidemiologic studies were undertaken and the activities of the family were reviewed in detail chronologically. Virus studies were made on the stools of 54 persons, and particular emphasis was placed on the children's associates. Virus was found in the stools of the youngest, unoperated child, in the stools of 6 cousins whom the children had visited and with whom they had been in intimate contact prior to their operations, and in the stools of 3 children of a family who were close playmates. The authors are convinced that tonsillectomy performed on an infected subject is the provocative factor in precipitating the bulbar type of poliomyelitis in a person who otherwise would probably escape with inapparent infection.

After reviewing the available literature and undertaking an analysis of statistics obtained from public health authorities, hospitals and a survey of a severe epidemic of poliomyelitis in Wichita, Kan., in 1940, Seydell[19] thinks it probably safe to say that tonsillectomy has no bearing on the incidence of spinal meningitis. A comparison of the statistical data in the literature showed that in all instances the percentage of tonsillectomized patients with the bulbar type is far greater than that of tonsillectomized patients with the spinal type. He holds that it will be necessary to institute other complete epidemiologic studies before this question can be answered, namely: Is the average person who has had a tonsillectomy more susceptible to poliomyelitis of the bulbar type than one who has not had this operation?

Like Seydell, Aycock[2] collected a vast amount of data on the relation of tonsillectomy to poliomyelitis from various hospitals, city and state health departments, numerous personal communications and 52 articles in the literature. Aycock writes that the results of his study are in keeping with other epidemiologic indications that some added circumstance determines the form of the disease which develops upon exposure to the virus of poliomyelitis and that this circumstance resides not so much in parasitic factors or in environmental conditions affecting exposure as in factors of autarcesis (the natural ability of the body to resist infection) in the host. There is a casual relationship between the removal of tonsils and the onset of bulbar poliomyelitis within the time interval corresponding to the incubation period of the disease. The statistics collected do not lend themselves to analysis whether or not the absence of tonsils predisposes to clinical poliomyelitis, with one exception. In this instance, cases of poliomyelitis gave a history of removal of tonsils with greater frequency than controls in the same area. It is shown, however, that the relative frequency of the occurrence of the bulbar, as compared with the spinal, form of poliomyelitis is greater at all ages in persons giving a history of previous tonsillectomy. Because of the numerical considera-

tions, the hazard of bulbar rather than spinal poliomyelitis in tonsillectomized individuals hardly constitutes in itself a contraindication to the operation. Although the risk should be recognized, the decision for the operation should rather be based upon the indications in the individual case. The selectivity seen in the occurrence of bulbar poliomyelitis following tonsillectomy and its relatively more frequent occurrence in tonsillectomized individuals comprise a demonstration that the nasopharyngeal mucosa may be the locus of at least one added circumstance which determines the outcome of exposure to the virus, and is important not only as indicative of the *modus operandi* of autarcesis, but as providing a means of prevention. Since this operation is practically always elective as to time, changing the season when it is done, so as not to coincide with the season of poliomyelitis prevalence, would eliminate numbers of cases of the highly fatal bulbar form of the disease.

In order that additional information on tonsillectomy and poliomyelitis might be gained, Page[15] consulted the records of Manhattan Eye, Ear and Throat Hospital and the Department of Health of the City of New York. As 1937, 1939 and 1941 were the years in which poliomyelitis was most prevalent, the patients who had tonsillectomies performed on them during these years were communicated with by mail; 27,849 cards were sent out by the Manhattan Eye, Ear and Throat Hospital, requesting that answers to the questions be written on a return postal card. On the return card were the patient's name, his age, his hospital number, the data of the tonsillectomy and the following questions: Have you had any illness since the tonsillectomy? What were the nature and the dates of illnesses, if any? A total of 8915 replies were obtained, and among them 1 instance of poliomyelitis was reported. For the same year (1937) in which 243 cases of poliomyelitis with 21 deaths were recorded by the New York Department of Health, 10,597 cards were sent out and 2545 replies were received. Similarly, in 1939 and 1941, cards were sent out. The data in the 7 replies that reported illnesses after tonsillectomies included spinal meningitis, tuberculous meningitis, and "infantile paralysis."

Radiation in Impaired Hearing. According to Crowe and Baylor,[5] a long-continued partial obstruction of the Eustachian tubes in children causes retraction of the tympanic membranes, impaired hearing for high tones with relatively good hearing for low tones and sometimes a total loss of hearing by bone conduction. In all the pharyngeal orifices of the Eustachian tubes of a group of 60 children nodules of lymphoid tissue caused partial occlusion. The location of the hyperplastic lymphoid tissue interfered with normal function of the tubes. The most satisfactory method of treatment they found to be irradiation with radium or Roentgen rays. After the hyperplastic tissue has been reduced and the tubal orifices appear normal, the hearing for high tones and for bone-conducted sounds often returns to normal, and it remains there as long as the Eustachian tubes are clear. After a cold, however, the original condition may recur, with consequent loss of hearing. If the causal condition is recognized and treated before the age of 15, hearing usually returns to somewhere near the normal level. After this age the results are far less satisfactory, because hyperplastic lymphoid tissue and partial tubal obstruction usually date from early childhood. After the age of 15, the secondary changes in the middle ear may be so advanced that they can be repaired by no treatment whatever. Irradiation does not permanently remove hyperplastic lymphoid tissue, but relatively small doses keep it in abeyance

during the age period in which it grows most actively. Crowe[6] finds that lymphoid tissue is so sensitive to radiation that the dosage employed in treatment is far below the amount that cause injury to the mucous membrane or surrounding structures. If used carelessly, radium therapy may be extremely dangerous. It should never be given in the presence of acute nasopharyngitis. Radiation is of no value in the treatment of chronic middle-ear suppuration, otosclerosis or any form of inner ear or nerve deafness. It is used for the sole purpose of reducing obstructing nodules of lymphoid tissue, decreasing the secretion of mucus and restoring the normal ventilating function of the Eustachian tube. For this reason radiation is more often beneficial in children than in adults.

A statistical study by Guild[11] and his associates of the hearing of 1365 Baltimore school children selected at random, between 8 and 14 years of age, revealed that impaired hearing for high tones is by far the commonest form of auditory defect in children, and occurs more often in boys than in girls, more often in winter than in autumn, and more often in older children. Of these children, 41.2% had some form of impaired hearing, but only 2.9% had a loss for conversational voice. More than half of the children had previously had their tonsils removed, but incidence of impaired hearing was almost the same in the 2 subgroups. No relationship existed between the incidence of hearing defects and condition of the teeth, height or weight for the age, or any of several other measurements made. The authors declare that irrespective of whether or not radon therapy, surgery or some other method of treatment proves best, the problem of the prevention of impaired hearing in children is of such magnitude that the coöperation of otologists, public health agencies, school authorities and family physicians will be needed for its successful practical solution.

Fricke and Brown[10] treated 82 patients with hypertrophied lymphoid tissue in the nasopharynx with radium, and of these 76 could be traced: 61 patients complained chiefly of deafness and tinnitus; in 15 the main complaints were frequent colds and severe sore throats. Hypertrophied lymphoid tissue, especially in the nasopharynx and the fossa of Rosenmüller, was present in all. Gamma rays of radium were employed. A straight metal rod ending in a brass tube containing radon was used. Definite and permanent improvement was obtained in 45 of the 76 patients, temporary improvement in 13 and no improvement in 18. The younger patients showed the best response to therapy.

Burnam[3] describes his technique in reducing the lymphoid tissue in the nasopharynx of children for improvement of hearing, but since his report Emerson[8] and his associates have designed simple appropriate instruments and established a technique they claim is within the reach of most clinics. It allows efficient irradiation of the lymphoid tissue at the orifice of the Eustachian tube with 25 mg. radium. Each needle is 20.3 mm. long, with an external diameter of 1.35 mm. Jones[13] describes and illustrates a radon applicator designed for office use which contains 100 millicuries of radon and finds its use for office treatment has proved satisfactory.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 20, 1945

Enzymological Investigations on Experimental Tuberculosis in Rabbits. CHARLES WEISS and NELLIE HALLIDAY (Laboratories, Jewish Hospital, Philadelphia). Several investigators, including Moen, have come to the conclusion that the specific toxic action of tuberculin upon hypersensitive tissues is probably not the result of an antigen antibody reaction. The discovery, by the present authors, of a selective inhibitory action of tuberculo-carbohydrate and tuberculo-phosphatid upon endocellular enzymes (Cathepsin II) derived from tissues of animals infected with tubercle bacilli throws new light upon this mechanism and suggests an enzymologic explanation, as follows: Since cathepsin is the enzyme which is concerned with the processes of cellular growth and repair, inhibition thereof leads to injury of the cells. Tuberculin is more toxic for tuberculous than for normal cells in tissue culture because two of its important constituents (phosphatid and carbohydrate) exert a selective inhibitory action upon the proteinases of the former.

Our observations may also throw light on the mechanism of caseation and softening. As pointed out by Jobling and Petersen, "caseation in tuberculosis is a form of coagulation necrosis in which the dead tissues rarely undergo autolysis, except as a result of secondary infection." It is quite likely that inhibition of autolysis is accomplished by the carbohydrate and phosphatid fractions of the tubercle bacilli.

Anticonvulsant Effects of Steroids. H. T. WYCIS and E. A. SPIEGEL (Department of Experimental Neurology, Temple Univ. Medical School). Continuing former studies (E. Spiegel, *Proc. Fed. Am. Soc. Exp. Biol., 2 (1), 1943*) anticonvulsant effects were observed on white female rats with androstenedione, dehydroandrosterone, desoxycorticosterone acetate, acetoxypregnenolone, progesterone and testosterone. The following substances had no or only a questionable anticonvulsant action: cholesterol, allocholesterol, cholesteryl bromide, epicholestanol, stigmasterol, stigmasteryl acetate, α-spinasteryl acetate, ergosterol, ergosteryl acetate, α-ergostenyl acetate, dehydrocholic acid, desoxycholic acid, Δ^5-3-acetoxy cholenic acid, sarsasapogenin acetate, pseudosarsasapogenin acetate, diosgenin acetate, pseudodiosgenin acetate, α-estradiol benzoate (progynon B), theelin in oil, 6(α)acetoxy-progesterone (amorphous modification), etio-cholan-3β-ol-17-one acetate, 5-pregnen-3β-ol-20-one acetate, 5,16-pregnadien-3β-

ol-20-one acetate, stilbesterol. The anticonvulsant dose lies rather close to or is identical with the hypnotic dose for testosterone, progesterone and desoxycorticosterone; a definite margin between these doses exists for adrostenedione, dehydroandrosterone and acetoxypregnenolone.

A Method for the Uniform Production of Experimental Gastric Ulcer in the Rat. HARRY SHAY, S. A. KOMAROV, M. GRUENSTEIN, H. SIPLET, and DAVID MERANZE (Medical Research Laboratory, Samuel S. Fels Fund, Philadelphia). After ligating the pylorus in properly fasted rats and allowing the gastric secretion to accumulate in the stomach, gastric ulceration will develop uniformly in the rumen, less often in the antrum, and least frequently in the body of the stomach. Ulceration results from the action of the accumulated unbuffered gastric juice in the stomach. The evidence for this is in the fact that ulcerations identical with those produced after pyloric ligation result in 3 to 4 hours after the gastric instillation in pylorus-ligated atropinized rats of: (*a*) human gastric juice; (*b*) rat's gastric juice; (*c*) an artificial acid-pepsin mixture similar in acidity and pepsin concentration to the natural gastric juice employed in the first two. Proper atropinization in the rat will inhibit gastric secretion for many hours. Furthermore, the lesions produced are clearly acid-pepsin ulcers because either neutralization of the acid or inactivation of the pepsin will prevent their formation. Because of these findings, we believe that this experimental method could be adopted readily for use as a rapid assay method for hormonal anti-acid or anti-ulcer agents. We have already utilized it for the study of acid neutralizing and anti-peptic agents *in vivo*.

A Study of the Intermediates of Acetate and Acetoacetate Oxidation With C^{13}. J. M. BUCHANAN, W. SAKAMI, S. GURIN and D. WRIGHT WILSON (Dept. of Physiological Chemistry, Univ. of Pennsylvania). It has been known for years that acetoacetic acid is a product of fat metabolism and it has been thought that fat metabolism is distinct from carbohydrate metabolism. However, Breusch and Wieland and Rosenthal have recently advanced the hypothesis that acetoacetic acid is metabolized by way of the citric acid (or tricarboxylic acid) cycle which is recognized as a metabolic pathway for the oxidation of carbohydrates. We have been able to study this hypothesis directly by using the heavy isotope of carbon to mark the carboxyl and beta carbon atoms in acetoacetic acid so that they could be followed as the compound was changed by enzymes in a tissue.

Isotopic acetoacetic acid was incubated with an homogenate of guinea-pig kidney. Using a suitable experimental procedure, we found isotopic carbon of acetoacetic acid in α-ketoglutaric and fumaric acids, compounds commonly recognized as intermediates in carbohydrate oxidation. Most of the isotope in α-ketoglutaric acid was in the carboxyl distal to the keto group. This indicates that cisaconitic acid may be an intermediate in acetoacetic acid oxidation but that citric acid is not. On account of the possibility that CO_2 might be formed from isotopic acetoacetate and might react to form isotopic fumaric acid, a control experiment was run which showed that such was not the case in our experiments.

As we have shown that acetoacetate may be metabolized by way of the tricarboxylic acid cycle, it was thought probable that acetate might be metabolized in the same way. Sodium acetate with excess C^{13} in the

carboxyl group was incubated with an homogenate of guinea-pig kidney and isotope was later found in succinic acid, an intermediate between α-ketoglutaric and fumaric acids. These findings indicate that acetate and acetoacetate are probably metabolized by the same pathway.

Subdivision of the Lung on the Basis of Bronchial Distribution. JOHN FRANKLIN HUBER (Dept. of Anatomy, Temple Univ. Medical School). From the smallest branches of the dividing bronchi, the irregular, thin-walled expansions form the air spaces from which gaseous exchange between the blood and air takes place. The total branching of each the right and the left bronchus (together with supporting tissue, blood-vessels, nerves and lymphatics) is a lung. It follows from this, that the ultimate or total branching of any bronchial branch, no matter what size, is a portion of the lung to which the name "bronchopulmonary segment" can be logically applied.

The largest bronchial branches form segments of the lung which are usually separated (at least in part) from each other by fissures and have, therefore, long been accepted as definite entities called lobes. On the right there are two fissures—three lobes, and on the left, one fissure—two lobes.

The next order, bronchial branches, also form segments which are definite entities in spite of the fact that they are usually not separated by fissures. These segments can be proved to be entities by several procedures, including injection of a colored gelatin mass into the segment, inflation of the segment and dissecting the segments free from each other. Added proof comes from the fact that extra fissures are seen which do separate these segments.

The author has suggested elsewhere (with Dr. Chevalier L. Jackson) that not only should the main bronchial branches be named according to their lung segment, such as "right upper lobe bronchus," but the next order branches be designated by the subdivisions of the lobes which they form, for example, "bronchus to the ventral segment of the right upper lobe."

BOOK REVIEWS AND NOTICES

ORGANIC CHEMISTRY. By LOUIS F. FIESER and MARY FIESER. Pp. 1112; numerous figs. Boston: D. C. Heath, 1944. Price, $8.00 (trade edition); $6.00 (college edition).

THIS is an excellent and modern work on organic chemistry which should prove to be of great interest to the biochemist as well as the organic chemist. The first portion of the book is devoted to a moderately elementary development of the subject and includes a good discussion of aliphatic and alicyclic chemistry. The latter half of the volume is a superb presentation of aromatic chemistry.

Interspersed throughout the book are essay chapters on special topics which will add immeasurably to the value of this text. These topics include Petroleum, Rubber, Fats and Waxes, Proteins, Microbiological Processes, Rôle of Carbohydrates in Biological Processes, Metabolism of Fats, Metabolism of Proteins and Amino Acids, and Dyestuffs. To those who are well acquainted with these fields, there will perhaps appear to be errors of omission which are obviously due to limitations of size and scope imposed upon the authors. Those who are unfamiliar with these fields will find that the Fiesers have summarized them in excellent fashion.

The publishers have done an excellent job; the binding, type, and paper are very satisfactory. There are remarkably few errors to be found. Mention should likewise be made that the book is very carefully indexed. In the Reviewer's opinion the Fiesers have made an outstanding contribution to the field.

S. G.

ARTHRITIS AND ALLIED CONDITIONS. By BERNARD I. COMROE, A.B., M.D., F.A.C.P., Associate in Medicine, Univ. of Penna.; Senior Ward Physician and Chief of the Arthritis Clinic, Hospital of the Univ. of Penna. Third Ed., enlarged and thoroughly revised. Pp. 1359; 329 ills. Philadelphia: Lea & Febiger, 1944. Price, $12.00.

THE ability of such a large book as this to reach 3 editions in 5 years loudly announces that it meets a need and suggests strongly that it meets it well. "Because of the generous assistance of numerous colleagues and friends, it has been possible to include in this 3rd edition 13 additional chapters and more than 100 new photographs. Extensive changes have been made in the text so that the subject matter is brought up to the minute; practically every page has been revised or rewritten in an effort to exclude antedated material and to include all newer important developments. New chapters have been added on such subjects as penicillin, psychogenic factors in rheumatic diseases, rheumatic manifestations of tropical diseases, recent advances in arthritis and allied conditions, common mistakes in arthritis and allied conditions, Dupuytren's contracture, diagnostic digest of the average arthritic problem for the general practitioner, effect of climate upon arthritis, occupational therapy, and differential diagnosis of rheumatoid arthritis for the practitioner." Also the chapter on massage has been enlarged and enriched with photographs. A new introductory chapter presents a diagnostic digest of the average arthritic problem for the general practitioner and another chapter on treatment from the same point of view. The text has been expanded by about 15% without increasing the size of the volume, by using a larger, though not unpleasant, page plate size. Treatment is emphasized throughout; the Reviewer, not a practicing physician, is not qualified to pass on such matters.

Some critics might take exception to some statements, especially in the

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chapter on sciatica, and query the relevancy of some of the presentations in a book on Arthritis—but in any case these are infrequent and often minor points. The "boxing" of chief items in this work, a novel and useful practice in medical books, has been continued from previous editions.

The illustrations, especially the frequent Roentgen rays, are excellent. In fact, the whole production, though complying strictly with wartime restrictions, seems more like the pleasanter and more satisfactory products of peacetime publishing.

One might well wonder how a busy physician could accomplish the work required by these 3 editions; but only if one did not know the Author.

E. K.

MEDICAL CLINICS OF NORTH AMERICA. Philadelphia Number. Symposium on Recent Advances in Medicine. November 1944. Pp. 1293 to 1608. Index for 1942–1944. Philadelphia and London: W. B. Saunders, 1944. Price, $16.00 per yr.

THIS number of the Medical Clinics is written by doctors from Philadelphia, and the material is presented in 2 parts. The first half of the volume consists of a symposium that includes Cardiovascular Diseases, Otolaryngology and and the Leukemias. Miller and Breitwieser have written a valuable survey for the field of Gastro-enterology, and Kern discusses the management of Rabies. Also covered are the use of Thiouracil and the epidemiology of acute respiratory tract infections, while Mudd presents a study of air conduction of disease.

The second portion of the volume is made up of work done by the Pennsylvania Hospital Unit on diseases of the tropics. The articles include the diagnosis and management of the Dengue Fevers, Leprosy, Scrub Typhus, Malaria, and the Dysenteries. Functional problems are discussed by Rush and Vander Veer who studied the Anxiety Neuroses as manifested in Gastrointestinal and Cardiovascular Symptoms.

M. H.

SOLDIER TO CIVILIAN. Problems of Readjustment. By GEORGE K. PRATT, M.D., Psychiatric Examiner, U. S. Armed Forces, Induction Center, New Haven, Conn.; Formerly Assistant Clinical Professor of Psychiatry, Yale University. Foreword by GEORGE S. STEVENSON, M.D., Medical Director, The National Committee for Mental Hygiene. Pp. 231. New York: McGraw-Hill Book Co., 1944. Price, $2.50.

THIS book is addressed "primarily to the families, and prospective employees of all returned service men." The treatise is discussed in the following chapters: Introduction. What Equipment Did the New Soldier Take with Him? What Did Military Service Do to the Former Civilian? How the Army Pre-Prevents Strains of Adjustment. Soldiers with Psychiatric Disabilities. The First Weeks at Home. Going Back to Work. Getting Reacquainted with the Family.

Emphasis is placed on the returning soldier who is physically or mentally handicapped. It is inferred that in the latter group are those who, through intellectual or emotional impairment, have become less efficient or less happy than they were previously. With no claim that his classification is scientific, the writer offers several groups. *The insanities or psychoses* affect subjects most of whom will require detention in mental hospitals. *The mentally defective* is one who has been endowed with less than the normal mental equipment, therefore, he must not be expected to assume the responsibilities of more fortunate individuals. *The psychopathic personalities* are different from the preceding group—they show character distortion; being unable to profit by experience, such individuals are apt to continue to be a grave problem to their families and to Society. *Structural diseases of the nervous system:* here may be shown either physical or mental impairment, for instance, as by fracture of the skull, or by syphilis of the central nervous system. Some such subjects may be treated and cared for at home. *The combat fatigue*

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disorders: these constituted the emotional group of World War I, then erroneously classed as "shell shock" patients, since but few had been exposed to shell fire. Under present-day methods, many are returned to full duty or to less demanding work. *The psychoneurotic:* this, by far the largest group, consists of those who show various anxiety states, psychosomatic disorders, obsessive or compulsive manifestations, or who are beset by fears and phobias. Of this group, it is believed that about 80% have had a latent predisposition to the disorder. A few may have been genuine malingerers and many have been discharged from the service for "psychopathic disability."

An Appendix discusses Community Services for Veterans. The suggestions and advice offered in this volume are excellent. N. Y.

OURSELVES UNBORN. An Embryologist's Essay on Man. The Terry Lectures. By GEORGE W. CORNER, Director of Department of Embryology of the Carnegie Institution of Washington and Professor of Embryology in Johns Hopkins Medical School. Pp. 188; 18 figs. Connecticut: Yale Univ. Press, 1944. Price, $3.00.

THE Author, an anatomist of high repute, here expounds the story of the development of the human embryo in its first few weeks of life ["When a man is born he is already 9 months old"], using photographs, beautifully designed diagrams, and reference material from other animals to portray the full picture in lucid form. "To the seeing eye the human embryo from egg to birth is an archive in which is written the evidence of its descent as an animal, a vertebrate, an amniote, a mammal, a primate; and it is an organic germ in which the gift of life is intrinsically bound up with the necessity of growth and of ineluctable change."

Included is an excellent presentation of the pathogenesis of embryonic disease, classified under (*a*) Defects of Fertilization, (*b*) Defects of the Maternal Environment, and (*c*) Defects of the Egg, the Sperm Cell and the Embryo. Here are discussed such timely matters as disturbances in tissue organizers, the tragic sequels of maternal German measles during the first months of pregnancy, and the genetic background of erythroblastic fetalis. It is a surprise to learn that in most mammals 20 to 50% of all conceptions succumb before birth, and that for humans the prenatal mortality is estimated as 1 out of every 3 pregnancies. "Those of us who survive are truly the elect, chosen from a larger multitude." A review of comparative anatomy and embryology shows that man differs from his close relatives the apes and monkeys in having a more general, less highly specialized anatomic structure, capable of widely diversified activities under the guidance of his superior free-functioning brain.

Dr. Corner has the imagination and wisdom to see the cultural relationships between the intricacies of his own highly specialized subject and the basic human problems which perplex all thoughtful minds. Modern embryology can offer pertinent significances to such intensely personal yet universal problems as the origin of individual man, the fore-ordaining of one's characteristic traits, and the relationship of our human bodies and souls to all other kinds of living creatures. He writes with grace and humor, and has a fine mastery of English style, which is an accomplishment possessed by but few leaders in American science. Never dull or confusing, his descriptions of the intricacies of embryonic and placental development are indeed easy to follow. This essay is thus more than a philosophically tinged exposition of a learned specialty; it can be deemed a proud contribution of modern biology to contemporary world literature. I. W.

HANDBOOK OF INDUSTRIAL PSYCHOLOGY. By DR. MAY SMITH. Pp. 304. New York: Philosophical Library, 1944. Price, $5.00.

IT is not this Author's purpose to furnish a detailed chronicle of industrial psychology, but one "to provide an introduction to the subject for those who are in some way responsible for others, or who have to get on with others."

Dr. Smith describes her branch of science as "the study of the conduct of those who exchange the work of their hands and brains for the means to live." The chapters are: Pioneer Work; Fatigue in Industry; The Environment; Finding the Job for the Person and the Person for the Job; Time and Motion Study; Temperaments, Particularly the Nervous; Why We Work; Measure of Human Well-being; General Hints on Methods of Investigation; Conclusions.

As to the chapter on "Temperaments," one finds nothing of greater merit in medical literature. This portion of her discourse is discussed as: history and classification; the nervous person; expression of nervousness in (*a*) work, (*b*) sickness, relations to people, (*c*) must the nervous person break down? Heretofore, the Author's work has been of signal service to the Board of Medical Research Council's Industrial Health Research. This contribution will be of especial significance to those who view with gravity the approaching post-war period. N. Y.

AMERICAN MEDICAL PRACTICE IN THE PERSPECTIVES OF A CENTURY. By BERNHARD J. STERN, PH.D., Lecturer in Sociology, Columbia University; Visiting Professor of Sociology, Yale University. Pp. 156. New York: The Commonwealth Fund, 1945. Price, $1.50.

THIS monograph presents the social aspects of medical practice as they have evolved during the past century, and in the first 2 chapters the relationship of the fundamental social changes in American life and the development of medical practice is discussed.

The changing pattern of medical practice is described in the next 4 chapters, dealing with the relation of the specialist and the general practitioner, the supply and distribution of physicians, the patient load carried by various types of medical practitioners, and the income of physicians. The facts revealed by a number of recent studies of medical practice are reviewed and discussed, particularly as indicating the need of revision in the present-day methods of medical service.

The final chapter on the distribution of medical services directs attention to the consumer of these services, and to his difficulties in financing present standards of medical care in communities where such care is obtainable. It is pointed out that the quantity and quality of medical care obtained by the consumer is largely determined by his economic status, and that although the lower economic groups have the greatest need for medical service, they get the least care. The medical care of Negroes is discussed at some length as an example of this paradoxical situation.

Unmet medical needs in this country are disturbing the American people and are stimulating legislative action as a means of solving these problems.

This monograph is the first of a series planned by "The Committee on Medicine and the Changing Order" of the New York Academy of Medicine, which hopes to provide a framework for an understanding of the current medical situation and its trends. The purpose of the Committee is admirably carried out in this first monograph; and if the same standard of excellence is maintained in those to follow, the series should be of much value both to the medical profession and to the general public in gaining a better understanding of the confused problems of medical service in our present-day complex Society. G. R.

THE TRIALS AND TRIUMPHS OF THE SURGEON, and Other Literary Gems. By J. CHALMERS DA COSTA, M.D., LL.D. Edited by FREDERICK E. KELLER, M.D. Pp. 401; no ills. Philadelphia: Dorrance, 1944. Price, $5.00.

THOSE who recall the eagerness with which much of medical Philadelphia flocked to hear the Author of these essays will be glad for this opportunity to refresh their memories. Those who never heard da Costa's speeches, full of brilliant allusions and trenchant, even biting, sarcasm about medical evils, could do worse than to become acquainted with these virile lively essays.

When attracted by such subjects as the unjustifiable longevity of objectionable people, or amused by "a man so stupid that he got splinters in his fingers if he scratched his head," and similar Bob Hope-isms, we should not neglect the deep truths that they sugar-coat. The newcomer must not be surprised at a style admittedly florid even a generation ago; idiots always gibber, fear produces its cold tremor, well-worn Gilbert and Sullivans do their turns, Tennyson's argosies of the skies and, especially *a propos* at this time, his Federation of the World, fulfill expectations by their presence. We miss the celebrated Blockley address, describing its ancient evils such as the "Board of Buzzards," whose members were "like corkscrews, the crookeder they were, the more pull they had!" One regrets the lack of any dating of the various items, for this book has durable worth; but this is a small matter compared to the positive values that Dr. Keller gives us in this interesting collection of essays.

E. K.

SHOULDER LESIONS. By H. F. MOSELEY, M.A., D.M., M.CH. (OXON.), F.R.C.S. (ENG. and C.), F.A.C.S., Montreal, Canada; Lecturer in Surgery, McGill University; Assistant Surgeon, Royal Victoria Hospital. Pp. 181; 70 figs. Springfield, Ill.: Charles C Thomas, 1945.

THE value of a monograph on "Shoulder Lesions" is readily appreciated by every one who meets the problems created by these lesions clinically. Shoulder pain is a frequent presenting symptom and often proves to be very baffling to the diagnostician and rather resistant to empirical treatment. Dr. Moseley's monograph is written simply and clearly. It reveals an extensive personal experience and a large amount of original observation. Chapter V on the "Calcified Deposits in the Rotator Cuff" will be of particular interest not only to specialists in this field but to medical practitioners in general and to medical students and house officers.

The chapter on the "Neurological Aspects of Shoulder Pain" and on Roentgen ray diagnosis and treatment have been contributed by colleagues who are specialists in these fields. The book should be of great value to the physician who wants a ready reference for helpful suggestions in the diagnosis and management of shoulder lesions.

J. R.

INTERNAL MEDICINE. Its Theory and Practice. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine, Tulane Univ. of Louisiana School of Medicine; Senior Visiting Physician, Charity Hosp., New Orleans, La. CONTRIBUTORS: Fuller Albright, Edgar Van N. Allen, David P. Barr, Harvey Bartle, Jr., Arthur L. Bloomfield, Leslie A. Chambers, Alan M. Chesney, Robert A. Cooke, Charles F. Craig, Ernest C. Faust, Grace A. Goldsmith, Frederic M. Hanes, William J. Kerr, Ralph A. Kinsella, Edward B. Krumbhaar, William S. McCann, James H. Means, Stacy R. Mettier, James A. Miller, Francis D. Murphy, John H. Musser, O. H. Perry Pepper, Maurice C. Pincoffs, Hobart A. Reimann, Charles Rupp, Fred M. Smith, Wesley W. Spink, Randall G. Sprague, Frank E. Stevenson, Edward A. Strecker, Cyrus C. Sturgis, Russell M. Wilder, George Wilson. Fourth Ed. Pp. 1518; 66 ills. Philadelphia: Lea & Febiger, 1945. Price, $10.00.

THIS standard work was originally written with two distinct objectives in mind. It was designed to give to the undergraduate student a textbook written by a limited number of well-qualified authors who would be able to present the essentials without allowing the work to become encyclopedic in size and impractical for study or handling. Its second purpose was to give to the practitioner of medicine a work of ready reference so documented that he could go at once to the sources of material or to the outstanding contributions of medical literature for more detailed information. In this 4th edition these purposes have been well fulfilled.

The new material which has been added to this work has required nearly 100 more pages than the previous edition, in spite of the deletions made in

many sections. These numerous changes and additions deal for the most part with the newer therapies; the sulfonamides, penicillin, thiouracil and many others. A certain amount of space has been devoted to the problems of war medicine, notably in conjunction with the protozoan and metazoan diseases and the acute infectious diseases. Military neuropsychiatric disabilities, war neurology and altitude sickness all receive due attention.

Nineteen of the 26 chapters are prepared by heads of medical school departments, the remaining 7 by authors who are heads of special divisions in departments of medicine. All of them are teachers of wide experience and authorities on the subject with which they deal. They know what to say and how best to say it and they are experienced writers as well as teachers. The subject matter is restricted to the practical rather than the theoretical. The material is well organized and its authorship vouches for its authority.

CONTAGIOUS DISEASES. A Guide for Parents. By W. W. BAUER, B.S., M.D., Director of Bureau of Health, Amer. Med. Assn.; Assoc. Editor of *Hygeia;* formerly Epidemiologist, Milwaukee Health Dept.; Lecturer in Public Health, Marquette Univ. Pp. 188; no ills. New York: Knopf, 1944. Price, $2.00.

THIS new edition is a worthwhile text which will make a place for itself in the health libraries of intelligent parents throughout the United States. After a fairly technical introduction, Dr. Bauer discusses quarantine and the Health Department, home nursing, and the more usual contagious diseases. He writes with common sense—as in the statement in Chapter IV, Hints for Home Nurses: "Drugs in 'candy' form have no place in a home where there are children;" and with humor—as when he says in Chapter VI, Getting Ready for Release, that the four postdisease ingredients for disinfecting the sickroom should be: "Hot soapy water, sunshiny fresh air, elbow grease and horse sense." He attacks the old superstitions, calls caution at the undisciplined use of new medical weapons and admits the limitations in contemporary medical knowledge.

In passing we would say that the index will prove more useful than the chapter headings which are not completely specific. We also feel that the suggestion in the chapter, Mad Dog, that you keep your dog quarantined for a month whenever suspected of a fight, shows that Dr. Bauer has had little contact with children and family pets!

Otherwise we find this an enlightening contribution to the field of popularized modern health knowledge. V. C.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc., F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, Univ. of Manitoba; Biochemist, Winnipeg General Hosp., etc. Fifth Ed. Pp. 415; 73 figs. (3 plates). Philadelphia: Blakiston, 1945. Price, $5.00.

THIS volume conforms to the general plan of these "Recent Advances" about which we have previously expressed ourselves in these columns. It "presents an up-to-date study of endocrinology . . . . Considerable attention is given to the clinical aspects of the subject . . . . In spite of the war . . . . important advances from many countries have been taken into consideration by the author . . . . The progress of chemistry makes it possible to isolate several of the 'internal secretions.' We have learned the chemical nature of these compounds and considerable about their physiologic activities. The logical treatment of conditions in the light of our new advance knowledge is indicated and the matter of correct therapeutic doses is discussed. Roentgen ray therapy has also been given attention. Among the outstanding advances discussed may be mentioned the following: Use of radioactive iodine; iodized proteins; function of parathyroid hormone and control of excretion of phosphat; steroid hormones of the adrenal cortex; new synthetic compounds with estrogenic activity; the posterior pituitary hormone; Cushing's syndrome; Fröhlich's syndrome; Simmonds' disease differentiated from anorexia nervosa; renin of the kidney, a hormone," etc. E. K.

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MALARIA: Its Diagnosis, Treatment and Prophylaxis. By WILLIAM N. BISPHAM, Colonel, U. S. Army, Retired. Pp. 197. Baltimore: Williams & Wilkins, 1944. Price, $3.50.

ACCORDING to the preface of this book, its purpose is "to give the physician a knowledge of the clinical features of malaria." Colonel Bispham apparently intended a masterly treatise, for he enlisted the aid of no less than 12 well-known and respected authorities, each of whom is said to have reviewed sections of the book. Some seem to have done so, judging from variations in the text. Others were perhaps too busy or too kindly to be justly critical. The result is a very uneven, rambling sort of discourse. It contains nothing new and much that is outmoded. Only 41 of its 175 pages are concerned with the clinical features of malaria. The remainder is taken up with history, geographic distribution, immunity, prevention, and other phases of the subject. The book cannot be recommended. H. R.

FAMILIAL SUSCEPTIBILITY TO TUBERCULOSIS. By RUTH RICE PUFFER. Pp. 106; 9 figs. and 21 tables. Boston: Harvard Univ. Press, 1944. Price $2.00.

THE purpose of this monograph is to present evidence relative to the rôle of familial susceptibility and exposure to the infection in the development of tuberculosis. The author reviews some of the outstanding experimental and epidemiologic studies which deal with these two factors not only in tuberculosis but also in leprosy, rheumatic fever, poliomyelitis and diabetes. The data accumulated from an intensive study over a 10-year period of the families of 541 white index cases in Williamstown County, Tenn., are summarized and evaluated.

Among the important observations detailed, the following may be noted. The incidence of the disease among siblings of tuberculous individuals was about twice as great as among siblings of the non-tuberculous consorts of these index cases, the control group. Likewise the tuberculosis mortality was greater in the former group. The varying and often contradictory reports in the literature relative to the incidence of the disease in consorts of tuberculous patients finds an explanation in Puffer's data for she found that consorts whose siblings are tuberculous develop the disease more frequently than consorts whose families are less affected by the infection. Data pointing in the same direction are given for parents and children of tuberculous cases. In all these instances the author is quite aware that it is often difficult to evaluate which of the two factors, susceptibility or exposure, plays the greater rôle. It is clear, however, that the data presented do lend weight to the concept that hereditary factors play a significant rôle in the disease.

Hence in any program for the control of tuberculosis it is not enough to examine all contacts of a tuberculous individual, it is also imperative, Puffer maintains, to investigate all the blood relatives of the tuberculous individuals in order to ferret out the tuberculous cases. She stresses the need of investigation of the factors underlying congenital resistance to the infection.

The book is an important contribution to the subject, is well written, comprehensively visualized and restrained in its conclusions. M. L.

CHILD CARE AND TRAINING. By MARION L. FAEGRE and JOHN E. ANDERSON. Sixth Ed. Pp. 320; with ills. Minneapolis: Univ. of Minnesota Press, 1944. Price, $2.50.

THE first two chapters summarize physical development in cursory fashion, but the bulk of this easy-to-read, excellent book deals most intimately and helpfully with the growth of the normal child's intelligence, emotions and behavior responses. It may be recommended to parents—and doctors—who feel the need of experienced counsel for child rearing problems at home.

I. W.

ARTERIAL HYPERTENSION. Its Diagnosis and Treatment. By IRVINE H. PAGE and ARTHUR CURTIS CORCORAN. Pp. 352. Chicago: Year Book Publishers, 1945. Price, $3.75.

IN 352 well-written pages the authors have clearly presented their ideas on the diagnosis and treatment of arterial hypertension. They are entitled to speak with authority on a subject about which they have worked, and thought, and written so much. That the book is still somewhat unsatisfying is not the fault of the authors but rather the result of the present unsettled state of the general problem of hypertension. Research workers in this field may be disappointed at certain omissions; for example, the endocrine system is given scant attention. One feels, however, that these omissions are intentional, and are part of the authors' plan in separating the wheat from the chaff, as they see it. For the clinician, the book offers a sincere, humane and well-integrated guide that should serve him well. The authors are to be congratulated especially upon their choice of the title "arterial hypertension" instead of the more generally used term of "high blood pressure." After all, the ordinary sphygmomanometer measures the arterial pressure only, and indirectly at that. J. G.

LEAD POISONING. By ABRAHAM CANTAROW, M.D., Associate Professor of Medicine, Jefferson Medical Coll.; Assistant Physician and Biochemist, Jefferson Hosp., Philadelphia; and MAX TRUMPER, PH.D., LT. COM., H-V (S), USNR., Naval Medical Research Inst., Bethesda, Md.; formerly Lecturer in Toxicology, Jefferson Medical Coll.; Consultant in Industrial Toxicology, Cynwyd, Pa. Pp. 264. Baltimore: Williams & Wilkins, 1944. Price, $3.00.

THE volume points out that lead poisoning, almost exclusively an occupational disease, with the exception of a small percentage of cases occurring in infants and young children, is probably the most prevalent industrial poisoning. The metal enters the body most commonly through the gastro-intestinal and respiratory tracts, occasionally through the skin (tetra-ethyl) and, rarely, from the subcutaneous tissues. Regardless of route of absorption or chemical or physical form, the primary distribution in the tissues is essentially the same, the bones eventually containing practically the entire deposit. There is a striking similarity of behavior of lead and calcium as regards their deposition and mobilization from bones. Lead is eliminated largely in feces and urine, and has been found in milk. High values for lead in the blood, urine and feces indicate only undue exposure, and must be correlated with the clinical picture before the diagnosis of lead poisoning can be made. Symptoms may first appear years after the last exposure, due to mobilization of the stored metal. Lead poisoning may be acute or chronic, the latter being encountered most frequently clinically. Development is characteristically insidious. Prominent clinical manifestations are gastro-intestinal symptoms, mild anemia and palsies. Recent studies indicate that the fundamental lesion of lead paralysis is in disturbed muscle physiology. Other significant findings are a lead line, and signs and symptoms of hypertensive encephalopathy.

The authors are convinced of "the necessity for a more general appreciation of the extent of the lead hazard and the importance of the early recognition of chronic lead poisoning." They have culled from an enormous literature material representing authoritative opinion, and on controversial questions have expressed a personal preference based on their own experience. There is some repetition, and at times the data of various investigators is so conflicting as to weaken any definite conclusion; but on the whole the 264 page book is very useful for reference work, and for those interested in a detailed knowledge of the subject. It covers in a thorough manner: (1) absorption, transportation, deposition and excretion of lead; (2) pathology and pathologic physiology; (3) clinical manifestations; (4) lead in blood, body fluids and excretions; (5) treatment of lead poisoning; (6) occurrence of chronic lead poisoning; (7) lead products in industry; (8) procedures for determination of lead. N. A.

XUM

NEW BOOKS

The Trials and Triumphs of the Surgeon. And Other Literary Gems. By J. CHALMERS DA COSTA, M.D., LL.D. Edited by FREDERICK E. KELLER, M.D. Pp. 401; no ills. Philadelphia: Dorrance, 1944. Price, $5.00.

The Abortion Problem. Proceedings of the Conference Held under the Auspices of the National Committee on Maternal Health, Inc., at the New York Academy of Medicine, June 19 and 20, 1942. By HOWARD C. TAYLOR, JR., M.D., Conference Chairman. Pp. 182; 3 ills. Baltimore: Williams & Wilkins, 1944.

Segmental Neuralgia in Painful Syndromes. By BERNARD JUDOVICH, B.S., M.D., Instructor in Neurology, Graduate School of Medicine, Univ. of Pennsylvania; Clinical Instructor in Neurology, Women's Medical Coll.: Chief of Neuralgia Clinics, Philadelphia General Hosp., Graduate Hosp., and Women's Medical Coll. Hosp., Philadelphia; and WILLIAM BATES, B.S., M.D., F.A.C.S., F.I.C.S., Professor of Surgery, Graduate School of Medicine, Univ. of Pennsylvania; Consulting Surgeon, Babies Hosp. and Philadelphia Home for Incurables; Consulting General Surgeon, Wills Hosp., Philadelphia. Pp. 313; 178 ills. Philadelphia: Davis, 1944. Price, $5.00.

A Textbook on Pathology of Labor, the Puerperium and the Newborn. By CHARLES O. MCCORMICK, A.B., M.D., F.A.C.S., Clinical Professor of Obstetrics, Indiana Univ. School of Medicine; Consulting Obstetrician to William H. Coleman Hosp. for Women, Indianapolis City Hosp., and Sunny Side Sanitarium. Pp. 399; 191 ills. St. Louis: Mosby, 1944. Price, $7.50.

The Story of a Hospital. The Neurological Institute of New York 1909–1938. By CHARLES A. ELSBERG, M.D., Chief of the Surgical Service (Emeritus), Neurological Institute, New York. Pp. 174; numerous ills. New York and London: Hoeber, 1944. Price, $3.50.

THIS is "a short account of the Neurological Institute from its simple beginnings in a small building to its more mature activities in the large and luxurious quarters at the Columbia University Medical Center. To the facts gathered from the records of the Board of Trustees and of the Medical Board, there has been added some notes from Dr. Elsberg's records." This booklet was written to "serve as a permanent record of the activities of a small group of medical pioneers."

Anatomy. As a Basis for Medical and Dental Practice. By DONALD MAINLAND, M.B., CH.B., D.Sc., F.R.S.E., F.R.S.C., Professor of Anatomy, Dalhousie Univ., Halifax, N. S., Canada. Pp. 863; no ills. New York: Hoeber, 1945. Price, $7.50.

Duodenal and Jejunal Peptic Ulcer. Technic of Resection. By RUDOLF NISSEN, M.D., Attending Surgeon, Jewish Hosp. of Brooklyn; Member, Medical Advisory Board, National Jewish Hosp. of Denver; formerly Professor of Surgery and Head of Dept. of Surgery, Univ. of Istanbul; and Associate Professor of Surgery, Univ. of Berlin. Foreword by OWEN H. WANGENSTEEN, M.D., PH.D., Professor of Surgery, Univ. of Minnesota; Surgeon-in-Chief, Univ. of Minnesota Hosp. Pp. 143. New York: Grune & Stratton, 1945. Price, $4.75.

Studies of Burns and Scalds. Medical Research Council. By L. COLEBROOK T. GIBSON, J. P. TODD, A. M. CLARK, A. BROWN, and A. B. ANDERSON. Pp. 204; many figs., charts and tables. London: His Majesty's Stationery Office, 1944. Price, 4s. 0d. (about 80 cents).

The Medical Clinics of North America. Chicago Number. Symposium on Neuropsychiatric Diseases. Pp. 271; 44 figs. Philadelphia and London: Saunders, 1945. Sold only by the year ($16.00).

A Laboratory Guide in Chemistry. By JOSEPH H. ROE, PH.D., Professor of Biochemistry, The School of Medicine, George Washington Univ., Washington, D. C. Pp. 191. St. Louis: Mosby, 1944. Price, $1.00.

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NEW EDITIONS

A Text-book of Psychiatry for Students and Practitioners. By D. K. Henderson, M.D. (Edin.), F.R.Fac. P. & S. (Glas.), F.R.C.P.E., Physician-Superintendent of The Royal Edinburgh Hosp. for Mental Disorders, and Professor of Psychiatry, Univ. of Edinburgh; and R. D. Gillespie, M.D. (Glas.), F.R.C.P. (Lond.), D.P.M. (Lond.), Physician for Psychological Medicine, Guy's Hosp., London; formerly Examiner in Mental Diseases and Psychology in the Univ. of London; Acting Air-Commodore, Royal Air Force Volunteer Reserve. Sixth Ed. Pp. 719. New York: Oxford Univ. Press, 1944. Price, $7.00.

Microbiology and Pathology. By Charles F. Carter, B.S., M.D., Instructor in Microbiology and Pathology, Parkland Hosp. School of Nursing, Dallas, Tex.; Director, Carter's Clinical Laboratory, Dallas, Tex.; Consulting Pathologist, St. Louis Southwestern Railway Hosp., Texarkana, Ark.; Consulting Pathologist, Mother Frances Hosp., Tyler, Tex.; formerly Director of Laboratories, Parkland Hosp. Third Ed. Pp. 777. St. Louis: Mosby, 1944. Price, $3.50.

This book, not so small as it looks, contains an amazing amount of information on various aspects of Microbiology and Pathology. Those who do not ask for much will not be disappointed. Though the words "for nurses" have been omitted from the title, the purpose remains. True-false questions at the ends of many chapters add a spice of novelty. The colored illustrations on coated paper are excellent, many black-and-whites on war paper had better have been omitted entirely.

Recent Advances in Endocrinology. By A. T. Cameron, M.A., D.Sc. (Edin.), F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hosp. Fifth Ed. Pp. 415; 73 figs., including 3 plates. Philadelphia: Blakiston, 1945. Price, $5.00.

Clinical Case-taking. Guides for the Study of Patients. By George R. Herrmann, M.D., Ph.D., Professor of Medicine, Univ. of Texas. Third Ed. Pp. 192. St. Louis: Mosby, 1945. Price, $1.75.

Principles of Chemistry. An Introductory Textbook of Inorganic, Organic and Physiological Chemistry for Nurses and Students of Home Economics and Applied Chemistry. By Joseph H. Roe, Ph.D., Professor of Biochemistry, School of Medicine, George Washington Univ.; formerly Instructor in Chemistry, Central School of Nursing, Washington, D. C. Sixth Ed. Pp. 403; 47 figs. (4 color plates). St. Louis: Mosby, 1944. Price, $2.75.

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